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CHANGES IN BRAIN VOLUME DURING ANESTHESIA: THE EFFECTS OF ANOXIA AND HYPERCAPNIA

J. C. WHITE, M.D.

M. VERLOT, M.D.*

B. SELVERSTONE, M.D.

AND

H. K. BEECHER, M.D.

BOSTON

This investigation was instigated by an unfortunate anesthetic complication which occurred in the Neurosurgical Service of the Massachusetts General Hospital in 1938. A young woman who was rapidly losing her vision because of a hypophysial adenoma that compressed the optic chiasm had a complicating severe bronchiectasis. Operation was therefore undertaken with only local infiltration anesthesia. The moment the tumor had been satisfactorily exposed, however, the patient lost her nerve and insisted that she be placed under general anesthesia. In view of the extensive bronchiectasis it was decided that a relatively low concentration of nitrous oxide with oxygen might be given. Since an intratracheal tube had not previously been inserted and it was deemed inadvisable to disturb the patient's position sufficiently to insert one, it appeared wiser not to use ether. With the onset of a minor degree of cyanosis as the gas was administered, the exposed cerebral hemisphere began to swell. Elevation and retraction of the frontal lobe at once became impossible, and the cerebral cortex soon herniated so that it protruded through the craniotomy opening. All thought of removing the adenoma had to be given up, and in order to replace the bone flap it was necessary to stop administration of the anesthetic and to permit the patient to breathe room air. As the oxygen saturation of the blood returned to normal, the cerebral swelling and herniation rapidly subsided.

*Dr. Verlot, who participated in the first half of this investigation, was a Fellow of the Belgian-American Educational Foundation from 1937 to 1939.

From the Neurosurgical and Anesthesia Services of the Massachusetts General Hospital, and the Surgical and Anesthesia Laboratories of the Harvard Medical School at the Massachusetts General Hospital.

A convenient instrument for the instantaneous decapitation of cats is a large size, double action tree pruner, illustrated in figure 2. After decapitation with this instrument, the great vessels in the side of the neck are cut across again with a sharp knife and the blood drained from the head by massaging the muscles of the neck under a stream of running water and compressing the eyeballs. The soft tissues of the head are then removed. It is best to open the orbits by

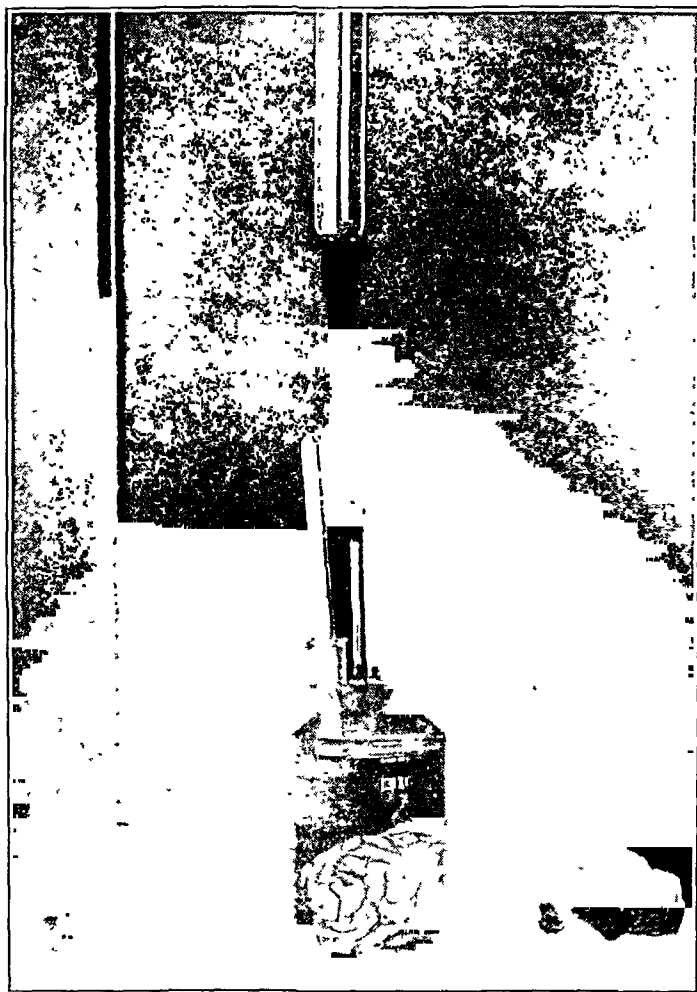


Fig. 1.—Apparatus for measuring brain and intracranial volume. The flask is filled from the buret through the capillary tube in its top by means of a lumbar puncture needle which permits air to escape. The thermometer to the left is for correction of temperature. The paraffin cast of the cranial cavity, to the right of the volumetric flask, appears smaller than the brain because the latter is magnified by the curved wall of the flask.

severing the orbital processes of the frontal and zygomatic bones and to remove the eyeballs. The pharyngeal structures are removed after the mandible has been disarticulated and the muscles separated from the base of the skull. The spinal

cord is cut flush with the foramen magnum before the atlanto-occipital joint has been disarticulated. The skull is then sawed around in the midline sagittal plane and split open like an oyster. With a little practice the brain can be removed with minimal injury to the olfactory lobes and only an occasional nick in the cerebellar hemispheres from the saw. The cranial nerves should be cut close to their respective foramina. It is important that the brain be removed from the skull immediately after death, since it may swell by imbibing cerebrospinal fluid.⁷

If the brain is removed and measured at once, this error is insignificant. The brain is transferred immediately to the volumetric flask, and its volume is determined by measuring the quantity of physiologic solution of sodium chloride which must be added to fill the flask. Cannon,⁸ Vandervael⁹ and Alexander and Looney¹ have shown that marked swelling occurs when the brain is placed in an isotonic or even in a hypertonic solution. Such imbibed fluid is included in our measurements and thus eliminated as a factor. It is also possible that varying amounts of cerebrospinal fluid in the ventricles may be a source of error. These cavities in the cat are so small that all ventricular fluid is probably expressed in the process of removing the brain from the skull, but the possibility of any error from retained fluid can be obviated by cutting the brain in two by a coronal section across the bodies of the ventricles. Measured in this manner the volume of the average adult cat's brain varies from 25 to 29 cc.

To measure the capacity of the cranial cavity one must reconstruct the skull by fitting the two halves together. This can be done accurately if the width of the skull has been determined before opening by caliper measurements just above the mastoids and at the anterior border of the orbits. It is necessary to use small wooden wedges to compensate for the section removed by the saw and to wire the two halves firmly and accurately together. Prior to reconstructing the skull we remove the dura and the bony tentorium, allowing an arbitrary amount of 0.1 cc. to represent the displacement of the tentorium. The reconstructed skull is then placed nose down in a closely fitting glass jar, and warm liquid paraffin is poured through the foramen magnum to fill the interior of the skull and embed it. Air bubbles which tend to form inside the cranium can be removed by scraping with a heated wire. After the paraffin has hardened (eight hours), it can be chipped away on the outside and trimmed flush with the foramen magnum (as was done previously with the spinal cord). The skull is

7. An unanesthetized normal animal (59 D) whose head was allowed to remain twenty-four hours and forty minutes at 2 C. before the skull was opened had a differential index of brain volume of 8.5 per cent (normal values, 9.8 to 11.1 per cent). It is suggested that this swelling was due in part at least to imbibition of cerebrospinal fluid by the brain. To check this hypothesis the brain of an unanesthetized animal (61 D) was placed in normal human cerebrospinal fluid at 2 C. for twenty-six hours. The brain increased in volume 0.81 cc., or 3.2 per cent of its original volume. This lowered the calculated differential index of the brain volume from a normal value of 10.1 to 7.9 per cent, a value which indicated definite swelling.

8. Cannon, W. B.: Cerebral Pressure Following Trauma, *Am. J. Physiol.* 6:91-121, 1901.

9. Vandervael, F.: Recherches sur l'imbibition du muscle et du cerveau dans les solutions dites physiologiques, *Arch. internat. de physiol.* 38:278-292, 1934.

then dissolved away in a bath of concentrated nitric acid, which leaves intact a paraffin cast of the cranial cavity. Excess of wax along the cut made by the saw is scraped away and any bubbles or holes due to wedges are carefully filled with plasticine. The volume of the cast is then measured in the volumetric flask; the determination differs in no way from that of the brain. On the average the intracranial capacity is some 30 cc. greater than that of the normal brain.

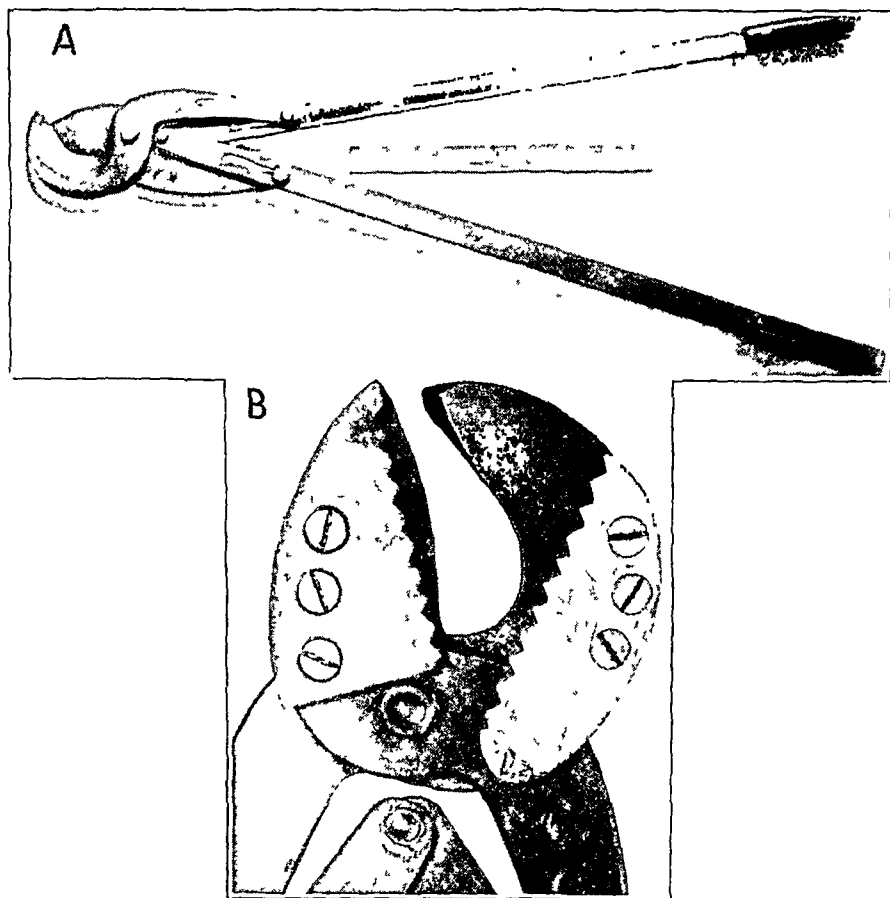


Fig. 2.—*A*, decapitating shears (large size tree pruner) with a foot rule for comparison; for decapitation with exsanguination the cutting blades are applied on the side of the occiput, but in addition the cervical vessels are subsequently severed with a sharp knife to insure free drainage of blood. *B*, the crushing blades; when these are applied beneath the occiput, the cervical tissues are so compressed that no loss of blood can take place.

We have expressed this difference in percentage of the total intracranial capacity; hereafter we shall refer to it as the differential index of brain volume. The exact computation is given from the actual figures for cat 55 D in table 1.

Determination of Blood Volume in Brain Tissue.—The volume of blood in the cerebral tissues has been determined by comparing the color reaction of hemoglobin with purified benzidine against a standard prepared from a sample of the

animal's own blood. This colorimetric hemoglobin method has been adapted by one of us (B. S.) as a modification of the method of Wu,¹⁰ later improved by Bing and Baker.¹¹ These determinations have been made both on the exsanguinated brains after determination of the brain volume (in this determination the physiologic solution of sodium chloride used to fill the flask is added to the brain) and on unexsanguinated brains. The unexsanguinated brains are prepared by decapitation with the tree pruner (fig. 2) turned so that the crushing teeth clamp off the tissues of the neck en masse. We have not observed back bleeding from the head with this method. The head is then frozen by means of solid carbon dioxide, the skull opened by means of a guillotine and the frozen brain substance removed piecemeal and weighed.

The brain tissue is minced with a knife and ground to a fine paste in a mortar with sand. If the brain volume has been determined, the physiologic solution of sodium chloride used is added, and the total volume in either case is brought

TABLE 1.—*Computation of the Differential Index of Brain Volume from the Figures for Cat 55 D*

$\frac{\text{Capacity of skull} - \text{volume of brain}}{\text{Capacity of skull}} = \text{differential index of brain volume}$	
Volume of brain	
Volume of flask.....	168.30 cc.
Physiologic solution of sodium chloride added.....	142.80 cc.
	25.50 cc.
Capacity of skull (paraffin mold)	
Volume of flask.....	168.30 cc.
Physiologic solution of sodium chloride added.....	139.22 cc.
	29.08 cc.
Correction for tentorium.....	.10 cc.
Capacity of skull.....	28.98 cc.
Volume of brain.....	25.50 cc.
Intracranial space not occupied by brain.....	3.48 cc.
Differential index of brain volume, or percentage of the intracranial space not occupied by brain.....	12.00 per cent

to 250 cc. with distilled water. A small amount of saponin is added to insure complete hemolysis. The resultant suspension is shaken well and allowed to stand overnight in a refrigerator. To correct variations in the hemoglobin content of the blood of individual animals, a standard solution of blood diluted 1:1,000 with distilled water is prepared for each animal from its own blood.

The colorimetric method employed is the benzidine technic of Bing and Baker as modified by Bing.¹² We have found a commercial benzidine reagent (Merck) to be satisfactory for the purpose and have not purified the crude base, as Bing did. The supernatant fluid over the brain suspension is used for the determination. This fluid remains cloudy, but since only 0.1 or 0.2 cc. is used for the determination and the final volume employed for reading is 25 cc., this has caused no

10. Wu, H.: Studies on Hemoglobin: III. An Ultra-Micro-Method for the Determination of Hemoglobin as a Peroxidase, *J. Biochem. (Japan)* **2**:189-194, 1923.

11. Bing, F. C., and Baker, R. W.: The Determination of Hemoglobin in Minute Amounts of Blood by Wu's Method, *J. Biol. Chem.* **92**:589-600, 1931.

12. Bing, F. C.: Purification of Benzidine and an Improved Reagent for Estimating Hemoglobin in Blood, *J. Biol. Chem.* **95**:387-388, 1932.

difficulty in colorimetry. The Duboscq colorimeter has proved most satisfactory for these determinations.¹³

Since we have assumed a uniform distribution of hemoglobin throughout the brain and the supernatant fluid and are unable to verify this assumption, we do not claim absolute accuracy for this method. Checks with blood samples the oxygen capacities of which have been determined by the method of Van Slyke and Neill¹⁴ have been accurate by this method within 12 per cent.

During the experiments a tracheal cannula was always inserted to maintain a wide-open airway, and attention was given to maintaining the dead space at about its normal size. The cannula was cleared of mucus when necessary, but no animals with a tendency to snuffles or other respiratory complications were used.

Rectal temperatures were recorded and not allowed to vary more than a degree by having the animal lie on an electrically heated pad when necessary.

Intracranial pressure was recorded by cisternal puncture, the animal lying on its side and the cistern needle being connected with a capillary manometer. This was filled with physiologic solution of sodium chloride, but precautions were taken to prevent the solution from entering the subarachnoid space, on account of Webster and Freeman's¹⁵ demonstration that the solution may cause a rise in intracranial pressure.

Arterial blood pressure was measured by the direct citrate method of recording with a glass cannula in the femoral artery and a U-shaped mercurial manometer.

Blood for determinations of oxygen and carbon dioxide was drawn under oil from the opposite femoral artery, and oxygen saturations and carbon dioxide content were determined by the methods of Van Slyke and Neill and Shaw and Downing.¹⁶

Atmospheres of varying oxygen content were made up in a large Douglas bag; oxygen and nitrogen were added in appropriate proportions from a spirometer, and then the final oxygen content of the mixture was measured by the Haldane gas analyzer described by Henderson.¹⁷ During inhalation the tracheal cannula of the animal was connected to the Douglas bag by a series of valves so that the gas breathed entered the trachea directly and was then exhaled into the room (fig. 3). To prevent building-up of carbon dioxide, a minimum of dead space was permitted. When ether anesthesia was induced with varying

13. The calculation by this method is simple when samples of 0.2 cc. are used.

$$\text{Centimeters of blood in the brain} = \frac{\text{Colorimeter setting on blood sample}}{4 \times \text{colorimeter reading on brain sample}}$$

This result is multiplied by 2 when, with the brains containing larger amounts of blood, only 0.1 cc. of supernatant fluid over the brain suspension is used.

14. Van Slyke, D. D., and Neill, J. M.: *The Determination of Gases in Blood and Other Solutions by Vacuum Extraction and Manometric Measurement*: I., *J. Biol. Chem.* **61**:523-573, 1924.

15. Webster, J. E., and Freeman, N. E.: *Studies on the Cerebrospinal Fluid Pressure in Unanesthetized Dogs*, *Ann. Surg.* **113**:556-571, 1941.

16. Shaw, J. L., and Downing, V.: *The Determination of Oxygen in the Blood in the Presence of Ether by a Modification of the Van Slyke-Neill Technique*, *J. Biol. Chem.* **109**:405-417, 1935.

17. Henderson, Y.: *Application of Gas Analysis*: IV. *The Haldane Gas Analyzer*, *J. Biol. Chem.* **33**:31-38, 1918.

degrees of anoxia, the closed system was further modified to permit addition of ether vapor to the prepared mixture of oxygen and nitrogen (fig. 3).

Depth of anesthesia was followed by observation of the presence or absence of the corneal reflex and of the response of a spinal reflex (contraction of the posterior thigh muscles when the central end of the cut sciatic nerve was stimulated by a faradic current). Every effort was made to keep these animals at a constant level of light surgical anesthesia.

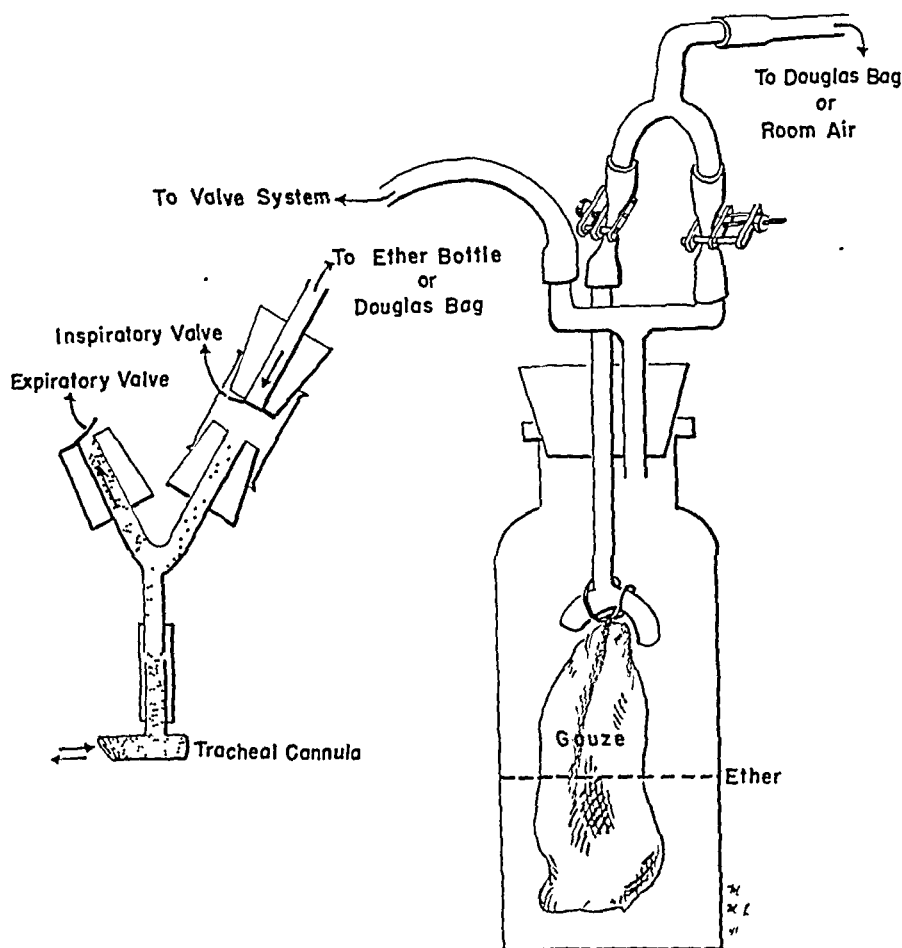


Fig. 3.—The inspiratory and expiratory valves shown in the diagram at the left permit the animal to inhale from the ether bottle or from the Douglas bag and to exhale into the room. The dead space, illustrated by the stippled area, must be reduced to approximately the volume of the upper part of the trachea and the nasal passages. A diagram of the ether bottle is shown on the right. By closing the left pinchcock and keeping the right open, the animal is made to breathe increasing amounts of ether-free atmosphere. The tension of ether vapor is increased by closing the cock on the right

CONDITIONS WHICH CAUSE SWELLING OF CEREBRAL TISSUE

Differential Index of Brain Volume in the Exsanguinated Normal Cat.—Four normal cats were instantaneously decapitated without anes-

thesia. The proportion of the cranial cavity not filled by brain in these animals is shown in table 2; it averages about 10.5 per cent of the total capacity of the cranium.

In our experiments we were careful to select adult cats. In human beings Rudolph has shown that the percentage of difference between cranial capacity and brain volume increases from 2.5 in infancy to 15 in old age (senile atrophy). In Alexander and Looney's¹ data on pathologic human brains the differential ratio varied from a volume of 29.3 per cent smaller than the cranial capacity in a patient with cerebral atrophy from Pick's disease to the opposite extreme in a patient with epilepsy, whose edematous brain filled the entire cranium. These extreme variations in human postmortem material are probably exaggerated by certain uncontrollable factors such as the duration and degree of capillary anoxia preceding death, the variable drainage of blood from

TABLE 2.—*Differential Index of Brain Volume and Blood Content of Cerebral Tissue of Unanesthetized Normal Cats (Brains Exsanguinated at Decapitation)*

Cat	Differential Index, per Cent	Cat	Blood Content, Cc.
45 D.....	9.9	112 D.....	0.21
46 D.....	11.1	113 D.....	0.19
47 D.....	11.1	114 D.....	0.19
61 D.....	10.1		
Average.....	10.5	Average.....	0.20

the brain after death and the varying length of time before the brain was removed from the cranium.⁷

Differential Ratio of Brain Volume Under Pentobarbital Sodium Anesthesia.—Pentobarbital sodium was injected intraperitoneally into a series of cats in initial doses of 40 mg. per kilogram of body weight, with increments of 5 to 10 mg. per kilogram of body weight as necessary to maintain a constant state of light surgical anesthesia. A tracheal cannula was inserted in every animal to insure an open airway; a warming pad was used to prevent the loss of body heat. Under these circumstances the brain remained approximately the same size as in the unanesthetized cat (up to fourteen hours in cat 51 D). In a series of 5 animals anesthetized with pentobarbital sodium the differential index of brain volume averaged 11.30 per cent (table 3). This differs by 0.80 per cent from the value for the unanesthetized animal (table 2). These figures have been analyzed by the method of Fisher¹⁸ for small series, and the difference was found to be insignificant.

18. Fisher, R. A.: *Statistical Methods for Research Workers*, ed. 6, London. Oliver & Boyd, 1938, chap. 5.

TABLE 3.—Data on Cats Under Light Pentobarbital Sodium Anesthesia

A. Cats Breathing Room Air							
Cat	Pento- barbital Sodium, Mg. per Kilogram of Body Weight	Duration of Anesthesia	Oxygen Saturation	Carbon Dioxide Content, Volumes per Cent	Cerebrospinal Fluid Pressure, Mm. of Solution of Sodium Chloride	Differential Index of Brain Volume, per Cent	Blood Content, Cc.
48 D	52	3 hr. 15 min.	Color good	71	11.7	0.11
49 D	40	5 hr. 6 min.	Color good	65	10.0
51 D	77.5	13 hr. 55 min.	Color good	113	10.1
52 D	63	3 hr. 20 min.	89.0 per cent	65.8	55	12.7	0.26
55 D	60	3 hr. 39 min.	92.6 per cent	39.0	62	12.0	0.24
Average.....						11.30	0.20

B. Cats Breathing 30 per Cent Oxygen and 5 to 10 per Cent Carbon Dioxide											
Cat	Pento- barbital Sodium, Mg. per Kg. of Body Weight	Duration of Anesthesia		Carbon Dioxide in In- spired Air, per Cent	Oxygen Satura- tion, per Cent	Carbon Dioxide Content, Volumes per Cent	Cerebrospinal Fluid Pressure			Differ- ential Index of Brain Volume	Blood Content, Cc.
		Total	Hyper- capnia				Onset	Maxi- mum	Final		
81 D	40	3 hr. 15 min.	24 min.	10	90	51.4	98	215	112	10.0
115 D	49	2 hr. 7 min.	32 min.	10	98.6	51.0	0.20
116 D	47	1 hr. 40 min.	35 min.	5.0	100	29.1	0.16
117 D	40	1 hr. 27 min.	43 min.	5.6	100	42.7	0.15

TABLE 4.—Data on Cats Under Light Pentobarbital Sodium Anesthesia

A. Cats with Anoxia												
Cat	Pento- barbital Sodium, Mg. per Kg. of Body Weight	Duration of Anesthesia		Oxygen in In- spired Air, per Cent	Carbon Dioxide in In- spired Air, per Cent	Oxygen Satura- tion, per Cent	Carbon Dioxide, Volumes per Cent	Cerebrospinal Fluid Pressure			Differ- ential Index of Brain Volume, per Cent	Blood Cont- ent, Cc.
		Total	Anoxia					Onset	Maxi- mum	Final		
63 D	50	4 hr. 4 min.	1 hr. 24 min.	9.3	0	79.8	28.2	56	59	59	5.6	0.11
64 D	50	5 hr. 35 min.	29 min.	5.1	0	42.0	17.1	80	116	57	6.3	0.22
65 D	50	4 hr. 58 min.	39 min.	9.3	0	80.6	35.5	83	195	80	7.4	0.34
66 D	50	6 hr. 32 min.	1 hr. 59 min.	9.3	0	70.7	34.8	55	134	134	6.9	0.19
Average.....											6.55	0.22
B. Cats with Anoxia and Increased Carbon Dioxide Tension												
93 D	60	3 hr. 26 min.	30 min.	9.6	8.3	41.6	46.8	55	150	104	6.8	0.32
95 D	72	5 hr. 11 min.	42 min.	10.2	9.5	54.7	51.6	56	131	124	7.2	0.30

On the other hand, when a cat anesthetized with pentobarbital sodium was made to breathe a nitrogen-oxygen mixture containing less than 10 per cent oxygen, there was a striking increase in the volume of the brain (table 4). The differential index of brain volume fell to an average of 6.55 per cent. As we pointed out, we do not know whether this fluid lost from the blood stream enters the interstitial spaces or causes swelling of the nerve and glial cells. An unexpected feature of the brain's tendency to swell during anoxia was the finding that maximal swelling

TABLE 5.—*Data on Cats Under Light Ether Anesthesia Breathing Room Air*

Cat	Duration of Anesthesia	Oxygen Saturation, per Cent	Carbon Dioxide Content, Volumes per Cent	Cerebrospinal Fluid Pressure			Differential Index of the Brain Volume, per Cent	Blood Content, Cc.
				Onset	Maximum	Final		
27 O	15 min.	Color good	9.4
31 O	1 hr. 50 min.	Color good	10.4
32 O	1 hr. 42 min.	Color good	8.0
82 D	3 hr. 32 min.	98.4	64.4	95	95	53	9.3	0.19
83 D	2 hr. 35 min.	95.5	51.0	98	102	68	10.0
84 D	2 hr. 23 min.	100.0	64.6	105	105	55	10.0
98 D	1 hr. 15 min.	95.5	42.8	0.30
108 D	0.25
109 D	0.28
Average.....							9.52	0.26

TABLE 6.—*Data on Cats Under Light Ether Anesthesia with Anoxia*

Cat	Duration of Anesthesia		Oxygen in Inspired Air, per Cent	Oxygen Saturation, per Cent	Carbon Dioxide Content, Volumes per Cent	Cerebrospinal Fluid Pressure			Differential Index of Brain Volume, per Cent	Blood Content, Cc.
	Total	Anoxia				Onset	Maximum	Final		
86 D	4 hr. 12 min.	36 min.	8	(Cyanosis	+++)	100	100	79	4.6	0.23
87 D	5 hr. 18 min.	50 min.	12.9	59.8	30.2	120	120	69	7.1	0.20
88 D	3 hr. 25 min.	50 min.	11.4	73.0	33.8	143	162	162	5.1
Average.....									5.6	0.215

may occur whenever the oxygen in the inspired air drops below 10 per cent and at any oxygen saturation of the arterial blood under 80 per cent. In cat 64 D there was no greater degree of swelling after a period of twenty-nine minutes in which these levels had been reduced nearly one half. Increasing the tension of carbon dioxide in the inspired air up to 10 volumes per cent does not cause any additional swelling of the anoxic brain tissue (table 4 B).

Differential Ratio of Brain Volume Under Ether Anesthesia.—When an intratracheal cannula and ether were used, with normal oxygen saturation of the arterial blood, the average index of brain volume in

6 cats was 9.52 per cent (table 5), compared with the normal of 10.50 per cent (table 2) for the unanesthetized animal. As in the series anesthetized with pentobarbital sodium, this apparent difference (0.98 per cent) was investigated by the method of Fisher for small series and found to be of no significance; by another method it was found to be of questionable significance.

When the etherized animal was made anoxic by breathing an atmosphere with the oxygen reduced below 13 per cent, swelling occurred as with the administration of pentobarbital sodium under similar basic conditions. These alterations in 3 cats are shown in table 6; the average differential index of brain volumes amounted to 5.6 per cent.

Differential Ratio of Brain Volume Under Nitrous Oxide Anesthesia.—When nitrous oxide was used, with which it is impossible to attain relaxation of the muscles without anoxia, swelling of the brain occurred in 2 cats which closely resembled that in the anoxic animals under anesthesia induced with pentobarbital sodium (table 7).

TABLE 7.—Data on Cats Under Nitrous Oxide Anesthesia

Cat	Duration of Anesthesia		Oxygen in Inspired Air, per Cent	Oxygen Saturation, per Cent	Carbon Dioxide Content, Volumes per Cent	Cerebrospinal Fluid Pressure			Differential Index of Brain Volume, per Cent
	Total	N ₂ O				Onset	Maximum	Final	
76 D	3 hr. 5 min.	40 min.	8.2	62.3	26.1	65	97	97	6.6
85 D	7 hr. 3 min.	42 min.	9.4	(Cyanosis +++)		102	253	207	7.3

In summarizing the effect of pentobarbital sodium and of ether on the volume of the brain there is strong evidence to show that no striking alterations in the permeability of the capillaries or in the content of intercellular or of intracellular fluid result from the action of these anesthetics of themselves. The slight apparent swelling occurring when ether is used was found not to be statistically significant, but further observations must be made to prove this point. Whenever anoxia is allowed to develop, large amounts of fluid escape from the capillaries and cause cerebral swelling sufficient to make intracranial operations difficult, if not impossible.

CONDITIONS WHICH CAUSE CEREBRAL VASCULAR ENGORGEMENT

The residual volume of blood in the brain after decapitation and drainage of the head as described on a foregoing page is remarkably constant and in a large series of cats averaged close to 0.2 cc. This held true whether decapitation was performed without an anesthetic or after the administration of pentobarbital sodium or of ether, regardless of whether the animal was normally oxygenated or anoxic. These findings

are recorded in tables 2, 3, 4, 5 and 6. The determinations were made as described under "Material and Methods."

Examination of table 8 shows that the blood content of the anoxic and of the normally oxygenated unexsanguinated brain is the same in the animal anesthetized with pentobarbital sodium as in the normal animal.¹⁹ In an animal anesthetized with ether it runs a good 0.2 cc. higher; this is doubtless due to the vasodilator effect of ether on the pial

TABLE 8—*Blood Contents of Unexsanguinated Brains of Cats*

Cat	Anesthesia	Duration of Anesthesia		Oxygen in Inspired Air, Volumes per Cent	Carbon Dioxide in Inspired Air, Volumes per Cent	Gases in Arterial Blood		Blood Content, Cc
						Oxygen Saturation, per Cent	Carbon Dioxide Content, Volumes per Cent	
		Total	Special Gas Mixture					
69 D	None			(Breathed room air)		(Color good)		0.49
70 D	None			(Breathed room air)		(Color good)		0.57
75 D	None			(Breathed room air)		(Color good)		0.40
105 D	None			(Breathed room air)		(Color good)		0.56
77 D	Pentobarbital sodium	2 hr		(Breathed room air)		(Color good)		0.48
78 D	Pentobarbital sodium	2 hr		(Breathed room air)		(Color good)		0.42
72 D	Pentobarbital sodium and anoxia	2 hr 1 min	28 min	6.4	0	32.0	22.8	0.52
75 D	Pentobarbital sodium and anoxia	2 hr 20 min	1 hr 3 min	9.3	0	81.2		0.39
67 D	Pentobarbital sodium and hypercapnia	4 hr 28 min	10 min	80	20	100.0	77.1	1.00
96 D	Pentobarbital sodium, anoxia and hypercapnia	57 min	31 min	10.4	10.4	36.4	51.3	0.83
89 D	Ether	50 min		(Breathed room air)		87.0	25.4	0.70
94 D	Ether	58 min		(Breathed room air)		95.0	30.1	0.82
104 D	Ether	37 min		(Breathed room air)		(Color good)		0.52
90 D	Ether and anoxia	2 hr 25 min	1 hr 1 min	10.6	0	58	33.6	0.64

vessels, which was first measured directly by Finesinger and Cobb.²⁰ Fortunately, this degree of added vascular engorgement in a subject under ether is too slight (less than 1 per cent of the total volume of the brain) to be noticeable during intracranial operations. From the data recorded in table 8 it is evident that anoxia is not a cause of cerebral congestion. Hypercapnia, increase in the carbon dioxide tension, on the other hand,

19. Wolff and Lennox,²¹ studying the pial vessels through a brain window, observed only a slight degree of vasodilatation accompanying extreme anoxia.

20. Finesinger, J. E., and Cobb, S: The Cerebral Circulation: XXXIV. The Action of Narcotic Drugs on the Pial Vessels, *J Pharmacol. & Exper Therap* 53:1-33, 1935

is a most effective vasodilator. This has been shown with regard to the pial vessels by Wolff and Lennox.²¹ In cat 67 D after the animal had breathed a mixture of 20 per cent carbon dioxide in 80 per cent oxygen for ten minutes the volume of blood in the cerebral vessels was twice that of a normal animal.

Figure 4 has been made by combining the data from the two sets of experiments, adding the additional volume of blood in the unexsanguinated brain to the total volume of the exsanguinated brain corrected

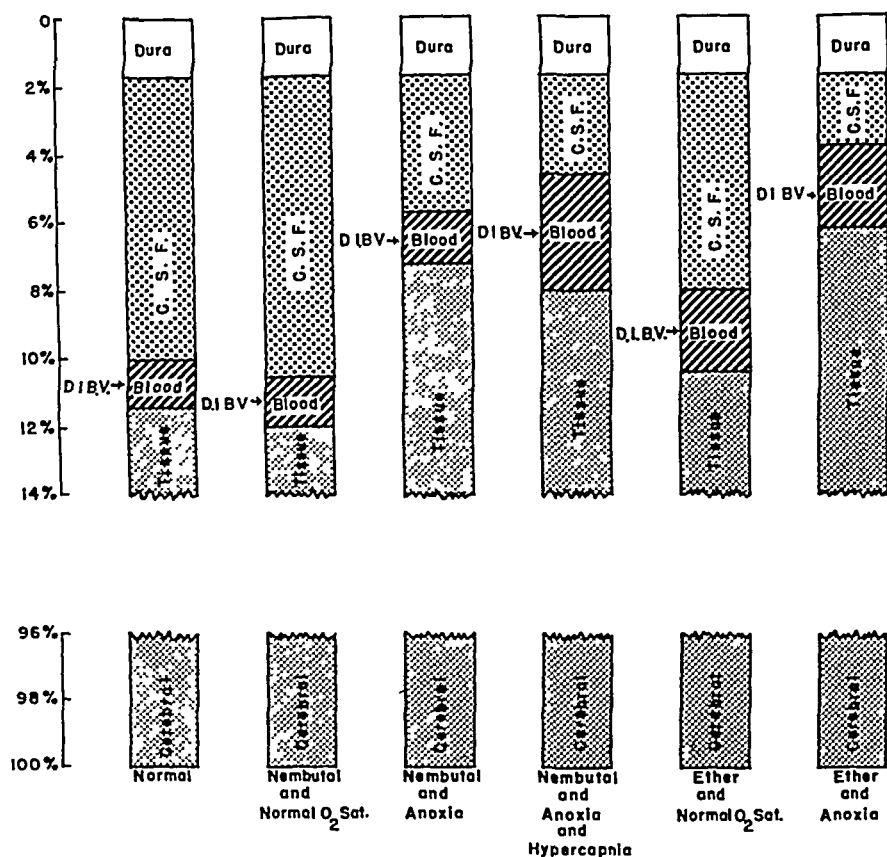


Fig. 4—Percentage of the cranial cavity occupied by cerebral tissue, blood and cerebrospinal fluid under varying conditions. The proportion of the total blood content which remains in the exsanguinated brain is indicated by the portion which lies below the arrow marking the differential index brain volume (*D.I.B.V.*). The apparently small volume of blood in the brain is explained at least in part by the fact that the blood content of the large venous sinuses is all included in the space occupied by the dura mater.

for its residual content of blood. It is apparent that in a subject anesthetized locally as well as with pentobarbital sodium or ether, the brain

21. Wolff, H. G., and Lennox, W. G.: Cerebral Circulation: XII. The Effect on Pial Vessels of Variations in the Oxygen and Carbon Dioxide Content of the Blood, *Arch. Neurol. & Psychiat.* **23**:1097-1120 (June) 1930.

fills approximately 91 per cent of the cranial cavity, a volume of which 89 per cent represents brain tissue and 2 per cent blood. The remaining space is filled by the dura with its large venous sinuses and the spinal fluid. The extent of the space occupied by spinal fluid which can be drained is of great importance to the neurosurgeon. In a subject under ether anesthesia with an obstructed airway, in whom both anoxia and hypercapnia are present, the brain may fill nearly the entire cranial cavity.

RELATIONSHIP OF CEREBROSPINAL FLUID PRESSURE TO BRAIN SWELLING

Changes in cerebrospinal fluid pressure in the cisterna magna were regularly observed and are tabulated in tables 3, 4, 5, 6 and 7. For convenience the alterations recorded during anoxia and hypercapnia are summarized in table 9. Examination of these readings shows that there is no correlation between the cerebrospinal fluid pressure and the degree of cerebral swelling during uncomplicated anoxia. In a certain number of these experiments there was a rapid rise in the cerebrospinal fluid pressure with the onset of anoxia, but more often than not the pressure in the final reading had fallen to a normal or near normal level. In the majority of these animals the final pressures were low. In others even the initial rises failed to take place. Furthermore, no correlation was apparent between the changes observed in spinal fluid pressure and the changes in systemic arterial blood pressure. These observations are not in accord with those of Maurer²² or Schaltenbrand,²³ who recorded definite rises in cerebrospinal fluid pressure during anoxia. In both sets of experiments, however, the atmospheric oxygen was reduced to between 6 and 4.6 per cent. In addition to a severe degree of anoxia, Maurer employed a respiratory pump. Furthermore, the observed increases in cerebrospinal fluid pressure were noted after only brief exposure to a reduced oxygen tension. We made most of our observations with animals breathing an atmosphere of from 10 to 8 per cent oxygen and over periods of thirty minutes or longer. A few of these animals had a sharp and maintained rise in pressure (table 9). Such a response is what one might at first expect in view of the Monro-Kellie²⁴ hypothesis. The theory postulates that because the brain and spinal

22. Maurer, F. W.: The Effects of Anoxemia Due to Carbon Monoxide and Low Oxygen on Cerebrospinal Fluid Pressure, *Am. J. Physiol.* **133**:180-188, 1941.

23. Schaltenbrand, G.: Luftdruck, Kreislauf, Atmung, und Liquordruck, *Acta aerophysiol.* (no. 1) **1**:61-65 and 65-71, 1933; (no. 2) **1**:41-49, 1934.

24. Monro, A.: Observations on the Structure and Functions of the Nervous System, Edinburgh, Creech & Johnson, 1783. Kellie, G.: Appearances Observed in the Dissection of Two Individuals. Death from Cold and Congestion of the Brain, *Tr. Med.-Chir. Soc., Edinburgh* **1**:84, 1824.

cord are incompressible and enclosed in the rigid cranium and vertebral canal there can be no increase in volume of brain tissue, blood or cerebrospinal fluid without a corresponding reduction in volume of one or both of the other components. Therefore when the brain tissue swells during anoxia there must be either a displacement of cerebrospinal fluid into the manometer or a reduction in the volume of the fluid or of the intracranial blood content. Our figures on intracerebral blood volume show that this remains relatively constant during anoxia (table 8). Therefore

TABLE 9.—Cerebrospinal Fluid Pressures of Cats Under Various Conditions

Cat	Anesthesia		Oxygen in Inspired Air, per Cent	Carbon Dioxide in Inspired Air, per Cent	Nitrogen in Inspired Air, per Cent	Oxygen Satur- ation, per Cent	Carbon Dioxide, Volumes per Cent	Cerebrospinal Fluid Pressure		
			Onset	Maxi- mum	Final					
63 D	Pentobarbital and anoxia	sodium	9.3	0	90.7	79.8	28.2	56	59	59
64 D	Pentobarbital and anoxia	sodium	5.1	0	94.9	42.0	17.1	80	116	57
65 D	Pentobarbital and anoxia	sodium	9.3	0	90.7	80.6	35.5	83	195	80
66 D	Pentobarbital and anoxia	sodium	9.3	0	90.7	70.7	34.8	55	134	134
81 D	Pentobarbital and hypercapnia	sodium	30.0	12.0	58.0	90.0	51.4	98	215	112
106 D	Pentobarbital and hypercapnia	sodium	30.0	10.0	60.0	95.5	41.2	65	95	45
93 D	Pentobarbital anoxia and hypercapnia	sodium,	9.6	8.3	82.1	41.6	46.8	55	150	104
95 D	Pentobarbital anoxia and hypercapnia	sodium,	10.2	9.5	80.3	54.7	51.6	56	131	124
82 D	Ether.....		(Breathed room air)			98.4	64.4	95	95	55
83 D	Ether.....		(Breathed room air)			95.5	51.0	98	102	68
84 D	Ether.....		(Breathed room air)			100.0	64.6	105	105	55
86 D	Ether and anoxia.....		8.0	0	92.0	(Cyanosis +++)		100	100	79
87 D	Ether and anoxia.....		12.9	0	87.1	59.8	30.2	120	120	69
88 D	Ether and anoxia.....		11.4	0	88.6	73.0	33.8	143	162	162
76 D	Nitrous oxide.....		8.2	0	91.8*	62.3	26.1	65	97	97
85 D	Nitrous oxide.....		9.4	0	90.6*	(Cyanosis +++)		102	253	207

* Nitrous oxide.

it is our opinion that compensatory mechanisms come into play during prolonged periods of anoxia and that the volume of the cerebrospinal fluid is thereby reduced. These mechanisms may include (1) an increase in the rate of absorption of the fluid by the normal channels, secondary to an elevated hydrostatic pressure, (2) direct imbibition of fluid on the part of the anoxic brain tissue and (3) decreased production of cerebrospinal fluid in anoxia. According to Flexner's²⁵ studies, the cerebro-

25. Flexner, L. B.: The Chemistry and Nature of the Cerebrospinal Fluid, *Physiol. Rev.* **14**:161-185, 1934.

spinal fluid is not a dialysate but a true secretion, which means that the cells of the choroid plexus must do actual work in the formation of the fluid. This in turn necessitates an ample supply of oxygen, and the cells of the choroid plexus are most susceptible to its lack.²⁶

Although we were unable to demonstrate consistent lasting elevation of the cerebrospinal fluid pressure in uncomplicated anoxia, there was a spectacular rise in the pressure when the carbon dioxide tension of the inspired air was raised. This is illustrated in table 9. In hypercapnia there is a rapid and consistent increase in intracranial pressure, which takes place concomitantly with the dilatation and congestion of the cerebral blood vessels. Although a secondary reduction was seen in some animals, the pressure rarely tended to drop back to the normal level.

COMMENT -

When ether is administered by the open cone method, swelling and congestion of the brain are frequent and serious hazards for the neurosurgeon. With intratracheal cannulation obstruction of the upper part of the respiratory tract is eliminated, and this complication does not occur. The experiments described show that anoxia and increase in carbon dioxide tension are important causes of swelling and congestion of the brain. When anoxia occurs from obstruction of the respiratory tract, failure of the respiratory center or an inadequate volume of oxygen in the gas mixture (nitrous oxide), permeability of the capillaries is increased, and fluid rapidly leaves the blood stream and enters the tissues. To decide whether this transudate enters the intercellular spaces or the cells themselves is beyond the scope of this paper, but in either event it is an equal handicap to the surgeon. This loss of fluid from the capillaries is not a peculiarity of the brain but takes place unnoticed throughout the body. Maurer,²⁷ studying the flow of lymph from the cervical and the cardiac lymphatics in the dog, noticed that reduction of the oxygen in the inspired air causes increased production of lymph. The increase begins as the oxygen saturation of the arterial blood is lowered to 75 per cent, and it reaches a maximum at 52 per cent. With increasing deprivation of oxygen the capillary endothelium first becomes increasingly permeable to water and crystalloids, later to the larger protein molecules and finally to the red blood cells. The same is true of

26. De Meio, R. H.; Kissin, M., and Barron, E. S. G.: Studies on Biological Oxidations; on Mechanism of Catalytic Effect of Reversible Dyes on Cellular Respiration, *J. Biol. Chem.* **107**:579-590, 1934.

27. Maurer, F. W.: The Effects of Decreased Blood Oxygen and Increased Blood Carbon Dioxide on the Flow and Composition of the Cervical and Cardiac Lymph, *Am. J. Physiol.* **131**:331-348, 1940.

lymph from the lung.²⁸ Landis, Jonas, Angevine and Erb²⁹ have shown that chemical injury of the capillary endothelium may result in a sevenfold increase in the rate of fluid filtration. Acute pulmonary edema, so often seen in patients dying of head injuries and brain tumors, is probably another manifestation of increased permeability of the capillaries during anoxia.

In addition to anoxia, engorgement of the cerebral vascular bed is a second factor which may cause the brain to swell. Cerebral congestion is not related to anoxia per se (table 8) but to an increase in the tension of carbon dioxide in the arterial blood. Wolff and Lennox have shown the importance of this factor as a vasodilator of the pial vessels; its action on the cerebral vascular bed in the cat is shown by the figures for cat 67 D, which demonstrate that during extreme hypercapnia the amount of blood in the cerebral vessels became double that in the vessels of the normal brain. Hypercapnia, like anoxia, may occur in the subject under general anesthesia because of obstruction of the respiratory tract or because of respiratory failure, or it may be due to faulty construction of the closed machines used in inducing anesthesia, which may have too great a dead space or inadequate facilities for removing carbon dioxide when rebreathing is used.

In most of these experiments the effects of hypercapnia were studied separately from those of anoxia by carefully preventing any accumulation of carbon dioxide in the blood while the animals breathed atmospheres deficient in oxygen or, on the other hand, by providing adequate oxygenation while they breathed atmospheres high in carbon dioxide. However, during complications in the actual course of anesthesia both factors usually operate together and make extremely difficult an adequate exposure of deep-lying structures, such as the pituitary, the third ventricle or the cerebellopontile angle. The reduction in free intracranial space is graphically illustrated in figure 4, where the space occupied by the various substances within the cranial chamber is given in percentages of the total cranial capacity. This shows that under satisfactory conditions there is no swelling or vascular engorgement with the use of pentobarbital sodium and only a slight increase in cerebral volume with the use of ether. This increase is apparently due to a slight relaxation in vascular tone. On the other hand, when severe respiratory obstruction prevents adequate intake of oxygen and output of carbon dioxide, the brain may undergo such extreme swelling and congestion that it fills the entire space within the cranium and herniates

28. Warren, M. F., and Drinker, C. K.: The Flow of Lymph from the Lungs of the Dog, *Am. J. Physiol.*, to be published.

29. Landis, E. M.; Jonas, L.; Angevine, M., and Erb, W.: The Passage of Fluid and Protein Through the Human Capillary Wall During Venous Congestion, *J. Clin. Investigation* **11**:717-734, 1932.

through an operative defect. Nitrous oxide should never be used as the sole anesthetic agent for craniotomies. To produce surgical anesthesia with this gas its concentration must often be raised to the point at which there is necessarily a drop in the oxygen saturation of the arterial blood below the critical level at which permeability of the capillaries is increased. When general anesthesia is used for intracranial operations, it is best to make routine use of the intratracheal tube. In this way obstruction of the respiratory tract can be prevented, an adequate amount of oxygen can be supplied, and carbon dioxide can be removed. If necessary to combat respiratory failure artificial respiration by intermittent insufflation of oxygen through the tube can be used. This useful device also prevents straining and elevation of intrathoracic pressure, factors which may increase the intracranial venous and capillary pressures and thereby increase bleeding from open vessels as well as cause a rise in fluid filtration from the capillary bed. The importance of this mechanism in the formation of edema has been shown by Krogh, Landis and Turner.³⁰

In addition to calling attention to the value of the intratracheal tube in anesthesia for operations on the brain, our work has several other important implications. It explains the importance of adequate oxygenation of patients with head injuries when cerebral swelling is already present. Schnedorf, Munslow, Crawford and McClure³¹ have shown that in experimental concussion in dogs and in cerebral injuries in human beings the oxygen saturation of the arterial blood may fall far below the critical level at which loss of fluid from the capillaries begins to take place. Nearly all the patients who died fell into this group, whereas those with an oxygen saturation above the critical level recovered. The relationship between the severity of an injury of the head and the arterial oxygen saturation is now being studied in this hospital, as is the effectiveness of oxygen therapy. The realization that reduction in the oxygen content of the inspired air is dangerous in cases of head injury has an important wartime bearing on the evacuation by airplane of persons with such injuries. Definite changes in volume of cranial contents probably begin to take place somewhere in the neighborhood of 11,000 feet, where the atmospheric oxygen is reduced to about 15 volumes per cent. At this level the arterial oxygen saturation drops to around 85 per cent in normal persons.³² The fact that wounded soldiers tolerate badly trans-

30. Krogh, A.; Landis, E. M., and Turner, A. H.: The Movements of Fluid Through the Human Capillary Wall in Relation to Venous Pressure to the Colloid Osmotic Pressure of the Blood, *J. Clin. Investigation* **11**:63-95, 1932.

31. Schnedorf, J. G.; Munslow, R. A.; Crawford, A. S., and McClure, R. D.: Anoxia and Oxygen Therapy in Head Injury, *Surg., Gynec. & Obst.* **70**:628-631, 1940.

32. Dill, D. B.; Talbott, J. H., and Consolazio, W. V.: Blood as a Physico-chemical System: Man at High Altitudes, *J. Biol. Chem.* **118**: 649-666, 1937.

port by air, because of the deleterious effect of anoxia on shock, is already known. When brain swelling is already present, its further increase by anoxia constitutes a serious risk.

These methods of studying volume changes which occur in the brain because of alterations in capillary permeability and because of vascular engorgement should be of value in the study and the treatment of head injuries, as well as of many other conditions which cause cerebral swelling and congestion. They are applicable to man as well as to experimental animals, although determinations made on the human brain post mortem are subject to uncontrollable errors, which have been discussed on an earlier page.

SUMMARY AND CONCLUSIONS

Quantitative methods of determining the volume and the blood content of the brain are described.

Neither swelling of tissue nor congestion of the cerebral vascular tree takes place in cats anesthetized with pentobarbital sodium provided there is an adequate airway. In cats anesthetized with ether there is no significant swelling of tissue, but there is a slight increase of blood content, due to a vasodilator effect on the cerebral vessels. This phenomenon does not appear to be sufficiently marked in man to cause any disturbance to the neurosurgeon.

From observations made on animals breathing low oxygen mixtures we conclude that anoxia results in an increase in intercellular or intracellular fluid, or both.

A rise in the carbon dioxide tension causes engorgement of the cerebral vascular tree.

If there is obstruction of the respiratory tract or respiratory failure, or if anesthetic mixtures are used with insufficient oxygen (nitrous oxide), the brain may so increase in size that intracranial operation is rendered difficult or impossible. This complication must be avoided by insuring adequate oxygenation of the tissues and by preventing an increase of carbon dioxide tension in the tissues. The intratracheal tube insures an open airway and permits the maintenance of a satisfactory supply of oxygen by insufflation if respiratory failure occurs.

This work on the behavior of the brain in anesthesia has important bearings on the treatment of patients with postoperative respiratory depression after craniotomy or cerebral trauma and on the transportation by plane at high altitude of soldiers with head injuries.

Dr. A. Baird Hastings, Kuhn professor of biological chemistry at the Harvard Medical School, and Dr. L. Alexander, neuropathologist at the Boston City Hospital, gave helpful criticism and advice. Miss Anna Murphy performed the blood gas analyses; Dr. Price Heusner, Miss Roberta Follansbee, Mr. J. R. Brooks and Mr. J. C. Goldthwaite helped in many of the experiments.

LOCAL IMPLANTATION OF SULFANILAMIDE AND ITS DERIVATIVES IN WOUNDS

ITS RELATION TO WOUND HEALING AND TO PERITONEAL ADHESIONS

SAMUEL P. HARBISON, M.D.

AND

J. ALBERT KEY, M.D.

ST. LOUIS

The bacteriostatic effects of sulfanilamide and its various derivatives are now too well known to require comment, and the rationale of the local use of these drugs in wounds has recently been reviewed by Key and Frankel.¹ Consequently, in this paper no attempt will be made to review the literature either on the effects of the drugs on various types of bacteria or on whether they are of value in combating infection when used locally in wounds. It is, however, a matter of growing interest to know whether or not the introduction of these drugs will inhibit the process of wound healing or will lead to the formation of adhesions in the peritoneum. This matter becomes especially important when one considers two stage procedures within the abdominal cavity; the difficulty encountered is often dependent on the presence of firm peritoneal adhesions.

It was noted by Key and Burford² that the introduction of powdered sulfanilamide and its derivatives into wounds did not interfere sufficiently with the healing of the wounds to be of clinical importance. However, in their experiments the tensile strength of the wounds was not tested. Taffel and Harvey³ introduced sulfanilamide crystals into small wounds of the stomach in a series of white rats and compared these animals with those of a series of controls on which similar operations were performed;

From the Department of Surgery, Washington University School of Medicine.

1. Key, J. A., and Frankel, C. J.: The Local Use of Sulfanilamide, Sulfapyridine and Sulfamethylthiazole, *Ann. Surg.* **113**:284-297 (Feb.) 1941.

2. Key, J. A., and Burford, T. H.: The Local Implantation of Sulfanilamide in Compound Fractures: Its Effect on Healing, *South. M. J.* **33**:449-455 (May) 1940; The Prophylactic Implantation of Sulfanilamide in Clean Operative Wounds for the Reduction of Postoperative Infections, *Surg., Gynec. & Obst.* **73**:324-332 (Sept.) 1941.

3. Taffel, M., and Harvey, S. C.: Effect of Local Application of Sulfanilamide upon Wound Healing, *Proc. Soc. Exper. Biol. & Med.* **47**:202-205 (June) 1941.

they found that there was no appreciable difference in the healing of the wounds in the two series as measured by the tensile strength.

In this paper we shall report: (1) a series of observations on the tensile strength of wounds in the abdominal wall and into the stomach and the duodenum into which sulfanilamide was implanted; (2) a series of experiments in which sulfanilamide and its derivatives were introduced into the abdominal cavity in rats to determine whether the drugs tended to cause peritoneal adhesions.

EFFECT OF SULFANILAMIDE ON THE HEALING OF WOUNDS IN THE ABDOMINAL WALL AND IN THE STOMACH AND THE DUODENUM

Adult guinea pigs and white rats were anesthetized with pentobarbital sodium, and symmetric incisions were made in the abdominal wall and carried through the peritoneum on each side. The wounds were then sutured in layers. Sulfanilamide crystals were placed in the wounds on the right side after the peritoneum had been sutured; those on the left were used as controls. In the guinea pigs it was possible to suture the wounds in three layers. In the rats the peritoneum and the rectus muscles were closed with the same continuous suture. The deeper structures were sutured with no. 000 and no. 00000 catgut, and the skin was closed with silk.

At various intervals of twenty-four hours to eleven days, the animals were killed, and the wounds were tested for tensile strength. In the guinea pigs a needle was inserted into the abdominal cavity, air was forced into the peritoneum under pressure, and the pressure at which the wound disrupted was noted. In the rats a strip approximately $\frac{1}{2}$ inch (1.3 cm.) wide was excised across the abdominal wall and through the wounds. The tensile strength of each wound was then tested by clamping the strip on either side of the wound and suspending the strip with a bucket attached to the lower end. The weight of the bucket was increased by adding water, and the point at which the strip of tissue ruptured was noted. Silk sutures were removed from all wounds before the test. After four days the influence of the catgut sutures could be disregarded.

Nine guinea pigs were used in the experiment, and these were killed at intervals varying from six to nine days after the operation. On inflation it was found that air was forced out of the abdominal cavity with rupture of the wounds when the pressure rose to from 40 to 320 mm. of mercury. There was no consistent difference between the wounds treated with sulfanilamide and the control wounds of the various animals. In some instances the side on which sulfanilamide had been implanted was stronger and in others the control side was stronger. The experi-

ment was not deemed satisfactory, because the wounds tended to give way gradually, and the air tended to get between the layers of the abdominal wall and because in some instances the wounds were complicated by mild infections, not sufficient to cause breaking down of the wound but tending to weaken it. Microscopic sections were made from all wounds. A few showed low grade infection, but the infection was no more frequent in the control wounds than in those in which sulfanilamide had been implanted. Microscopically there was no demonstrable difference between the wounds treated with sulfanilamide and the control wounds either in foreign body reaction or in the extent of fibroplasia.

In the 12 rats, wounds were made on each side of the abdominal wall, and then strips $\frac{1}{2}$ inch (1.3 cm.) wide were excised through the wounds and tested directly for tensile strength. The strips from wounds seven or more days old supported 410 to 1,400 Gm., depending on the age of the wound. Although the average tensile strength of the control wounds was slightly greater than that of the experimental wounds, in some instances the wounds treated with sulfanilamide were stronger. Sections of these wounds also showed a few mild infections without actual suppuration, and it was felt that these infections were sufficient to alter the tensile strength. Microscopically there was no demonstrable difference between the two series of wounds. It is to be noted that under the conditions of these experiments, in which no dressing was kept on the wounds, the implantation of sulfanilamide at the time of operation did not prevent the development of stitch abscesses in the abdominal wounds.

While these experiments were not conclusive, they indicated that the presence of a moderate amount of sulfanilamide in the wound did not seriously interfere with wound healing and that after seven or nine days the wounds were as strong as those in which the sulfanilamide had not been implanted. Previously, it was felt that the sulfanilamide powder, especially if used in too large amounts, might interfere mechanically with the healing of the wounds by tending to separate the raw surfaces.

We did not extend the series to include a large number of animals, because our experience with the two aforementioned small groups convinced us that a satisfactory determination of the actual tensile strength of healing wounds could not be made in these small animals and that for such a determination a large series of larger wounds in dogs or cats would be necessary. We performed some similar experiments on rabbits and found that these also were unsatisfactory animals for this problem. However, our small number of experiments convinced us that the presence of a moderate amount of sulfanilamide in the wound did not materially affect the rate of healing or the tensile strength of the wound.

In our experiments on viscera dogs were used, because it was felt that guinea pigs and rats were too small and that the tissues were so delicate that the wounds could not be uniformly and accurately sutured.

With the dog under general anesthesia, the abdomen was opened, and incisions 3 cm. long were made in the stomach and the duodenum. These wounds were sutured in two layers with no. 00000 catgut attached to atraumatic intestinal needles. In this series 10 animals were used (20 wounds). Ten of these wounds were used as controls, and in 10 sulfanilamide powder was introduced after the mucosa had been sutured. At intervals of five to eleven days the animals were killed in pairs, the viscus was tied off, and the tensile strength of the wounds was tested by inserting a needle into the lumen of the viscus and inflating the viscus under pressure. The tension was measured in millimeters of mercury according to the technic used by Harvey.⁴

It was found that the stomach wounds ruptured at tensions of 70 to 140 mm. of mercury, while wounds in the duodenum resisted tensions of from 160 to 520 mm. of mercury. In some instances the control wounds were stronger than those in which sulfanilamide was implanted and in other instances the wounds in which sulfanilamide had been implanted were stronger than the control wounds. It was noted that there was considerable difference in the strength of the wall of the viscus of the various animals. In 4 animals the normal lower part of the duodenum was tied off, and it was found that this could be ruptured by tensions of from 400 to 500 mm. of mercury. The eleven day old wounds of both control and experimental animals tended to reach this strength. These experiments indicated that the introduction of sulfanilamide into the wound did not appreciably delay the healing or decrease the tensile strength of the wound. It was also noted in these experiments that in those animals in which sulfanilamide had been introduced there was less reaction around the wounds than was present in the control animals. A preliminary report on these experiments has been published.⁵

DO SULFANILAMIDE AND ITS DERIVATIVES CAUSE PERITONEAL ADHESIONS?

The question whether sulfanilamide and its derivatives tend to cause peritoneal adhesions was suggested by the discovery of dense adhesions in the abdomen during the second stage of a two stage procedure for resection of the cecum. Sulfanilamide powder had been inserted after the preliminary ileocolostomy. Were these adhesions due to infection or to the presence of the powdered drug? To answer this question experiments were carried out with a group of rats. With the rat under general anesthesia, the abdomen was opened and with a small blunt

4. Harvey, S. C.: The Velocity of the Growth of Fibroblasts in the Healing Wound, *Arch. Surg.* **18**:1227-1240 (May) 1929.

5. Harbison, S. P.: Crystalline Sulfanilamide and Wound Healing, *Bull. St. Louis M. Soc.* **35**:146-147 (Dec.) 1940.

curet approximately 500 mg. of sterile crystalline or powdered sulfanilamide or one of its derivatives was introduced into the abdominal cavity. The drugs were spread around the cavity by sweeping the curet back and forth; this caused a moderate amount of trauma to the viscera and to the abdominal wall and served to distribute the powder generally over the surface of the exposed viscera. The drugs used were sulfanilamide, sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole), sulfadiazine (2-sulfanilamidopyrimidine) and a mixture of two parts of sulfanilamide and one part of sulfathiazole. Ten animals were used for the study of each drug and the mixture, and 10 were used as controls. In the latter the curet was swept about the abdominal cavity without introduction of the drugs in order to produce the same amount of mechanical trauma.

In all instances the wounds healed by first intention. One animal of the group treated with sulfathiazole died on the twenty-second day from causes unknown. There were no adhesions observed at autopsy. At the end of twenty-eight days the other animals were killed. Careful examination of the peritoneal cavity showed no adhesions in any of the animals in which the drugs had been introduced into the abdominal cavity, except for an occasional filmy adhesion of the omentum to the operative wound. Similarly, there were no adhesions in the controls, except in 2 instances in which the omentum was adherent to the site of the abdominal wound. Microscopic sections of the peritoneum of some of the animals in each group were made. Study of these sections showed no difference between the control animals and the experimental animals. In all the peritoneum appeared to be normal. In a preliminary report of a study of the early peritoneal response to treatment with these powdered drugs made by smears of the exudate obtained by aspiration,⁶ Throckmorton⁶ observed no specific reaction.

CONCLUSIONS

1. The local implantation of a moderate amount of sulfanilamide powder in wounds of the abdominal wall and in wounds of the stomach and the duodenum of experimental animals does not appreciably interfere with the healing of these wounds. Such wounds when tested show approximately the same tensile strength as similar wounds in which sulfanilamide and its derivatives have not been implanted.

2. The introduction of sulfanilamide, sulfathiazole, sulfadiazine or mixtures of sulfanilamide and sulfathiazole into the peritoneal cavity does not tend to cause adhesions in the rat.

6. Throckmorton, T. D.: The Peritoneal Response to Powdered Sulfonamide Compounds, *Proc. Staff Meet., Mayo Clin.* **16**:423-425 (July 2) 1941.

HISTOLOGIC CHARACTER OF THE UNDESCENDED TESTIS AFTER PUBERTY

ITS SIGNIFICANCE WITH REFERENCE TO THE PERFORMANCE OF ORCHIOPEXY

CHARLES E. REA, M.D.

ST. PAUL

The purposes of this paper are (a) to make a histologic study of the undescended testis in order to arrive at a better concept of the histologic character of the testis at various ages, (b) to determine how long enough of the germinal epithelium survives to justify orchiopexy and (c) to correlate this histologic and clinical knowledge in an attempt to formulate a rational plan of treatment for older cryptorchids.

The histology of the prepubertal testis has been discussed in detail elsewhere;¹ suffice it to say here that up to puberty there are no differences discernible grossly or microscopically between the normally descended and the undescended testis. Concerning the histologic character of the postpubertal ectopic gonad there have been but few reports. Maréchal,² Rawlings,³ Vidal⁴ and Burghard⁵ expressed their opinion that in the majority of cases the postpubertal retained testis is capable of spermatogenesis. On the other hand, Bland-Sutton⁶ and Curling⁷ stated that most cryptorchids are sterile. It should be said, however, that there is undeniable clinical evidence that cryptorchids may be

From the Department of Surgery, University of Minnesota Medical School.

1. Wangenstein, O. H.: The Undescended Testis: An Experimental and Clinical Study, *Arch. Surg.* **14**:663 (March) 1927; The Surgery of the Undescended Testis, *Surg., Gynec. & Obst.* **54**:219, 1932; The Undescended Testis: Its Fate After Satisfactory Scrotal Anchorage, *Ann. Surg.* **102**:875, 1935. Rea, C. E.: Functional Capacity of the Undescended Testis, *Arch. Surg.* **38**:1054 (June) 1939.

2. Maréchal, A., cited by Wangenstein.¹

3. Rawlings, L. B.: The Surgical Treatment of the Incompletely Descended Testicle, *Practitioner* **81**:250, 1908.

4. Vidal, E.: Quelques points du traitement des ectopies testiculaires, *Assoc. franç. de chir., Proc.-verb.* **19**:738-745, 1906.

5. Burghard, F. F.: Operations on the Male Genital Organs, *Oxford Surg.* **4**:39, 1918.

6. Bland-Sutton, J.: The Value of the Undescended Testis, *Practitioner* **84**:19, 1910; in discussion on Hobday, F.: Cryptorchidism in Animals and Man, *Proc. Roy. Soc. Med.* **17**:3, 1923.

7. Curling, T. B.: A Practical Treatise on the Diseases of the Testis, London, 1878.

fertile. Uffreduzzi⁸ claimed that 10 per cent of untreated cryptorchids show evidences of fertility. However, Caulk⁹ stated his belief that such fertility is short lived and seldom lasts five to ten years after puberty in untreated cryptorchids. From the reports of Coley,¹⁰ Wangenstein, MacCollum¹¹ and Rea there can be no question but that cryptorchids may have spermatozoa in the semen after operation.

In a study of 51 undescended testes, Felizet and Branca¹² observed spermatogonia in 16, spermatocytes in 12 and spermatids in 2, but they never found spermatozoa. Odiorne and Simmons¹³ expressed their opinion that spermatogonia and spermatocytes can be distinguished in many cases and that in only a few can spermatozoa be seen. In their examination of 9 undescended testes of adult patients, spermatozoa were found in 4; 1 patient was 30 years of age, and the other patients were 16, 16 and 20 years of age, respectively. Godard¹⁴ studied 5 retained testes removed from patients 19 to 25 years of age. In none were there signs of spermatogenesis. In the ectopic gonads of 16 patients on whom Corner¹⁵ performed orchidectomy no spermatozoa were seen; however, it should be mentioned that the age of an unstated number of patients was below puberty. Wangenstein stated his view that the occurrence of spermatozoa in the retained testes of young patients is decidedly unusual and that active spermatogenesis is probably never maintained. Pace¹⁶ reviewed histologically 24 undescended testes removed at operation at the Mayo Clinic. He found that the germinal epithelium in 4 of the 5 testes removed from patients in the fourth decade of life and in 2 of the 4 testes from patients in the fifth decade was fairly

8. Uffreduzzi, O.: Die Pathologie des Hodenretention, Arch. f. klin. Chir. **101**:150, 1913.

9. Caulk, J. R.: Treatment of Undescended Testicle, Surg., Gynec. & Obst. **35**:637, 1922.

10. Coley, W. B.: The Operative Treatment of the Undescended or Mal-descended Testis with Special Reference to End Results, Surg., Gynec. & Obst. **28**:452, 1919.

11. MacCollum, D. W.: Clinical Study of the Spermatogenesis of Undescended Testicle, Arch. Surg. **31**:290 (Aug.) 1935.

12. Felizet, G., and Branca, A.: Histologie du testicule ectopique, J. de l'anat. et physiol. **34**:589, 1898; Le testicule ectopique après la puberté, Comp. rend. Soc. de biol. **50**:967, 1898; La spermatogénès dans le testicule ectopique, Compt. rend. Soc. de biol. **54**:918, 1902.

13. Odiorne, W. B., and Simmons, C. C.: Undescended Testicle, Ann. Surg. **40**:962, 1904.

14. Godard, M. E.: Etudes sur la monorchidie et la cryptorchidie, Compt. rend. Soc. de biol. **8**:315, 1856.

15. Corner, E.: The Value of the Imperfectly Descended Testis: The Advisability of Operation and the Value of Operations Performed for Its Relief, Brit. M. J. **1**:1306, 1904.

16. Pace, J. M.: The Histology and Pathologic Anatomy of the Retained Testis, Proc. Staff Meet., Mayo Clin. **10**:726, 1935.

well preserved. The locations of the testes in patients in the fourth decade of life were abdominal, inguinal, at the external ring, and just outside the external ring, respectively; the location of the 2 testes from patients in the fifth decade were the inguinal canal and just outside the external inguinal ring, respectively. Páček found that the atrophy and degeneration of the testicular tubules progressed with age in cases of ectopy.

Thus, a review of the literature reveals few complete studies in which the age of the patient, the location of the retained gonad and its histologic appearance are correlated. In fact, so fragmentary is the histology of the postpubertal testis that the whole subject can well be reinvestigated.

MATERIAL

Forty-six undescended testes from patients past puberty were available for study. The specimens were obtained from the Ancker Hospital, St. Paul, the Minneapolis General Hospital, the University Hospitals, and the department of pathology of the University of Minnesota Medical School.¹⁷ These organs had been removed at autopsies or at operations because of atrophy, pain, suspected tumor, inability to bring the retained testis into the scrotum, large associated hydrocele or hernia. In some instances sections for biopsy taken during the course of orchiopexy at the University Hospitals were obtained; these specimens had been fixed in 10 per cent solution of formaldehyde U. S. P. and stained with hematoxylin and eosin.

The cases of undescended testis have been analyzed from the point of view of the age of the patient, the location of the undescended testis and the gross and the microscopic appearance of the testis. Since puberty in the male occurs between the ages of 13 and 15 years without regard to race, climate or individual differences,¹⁸ only those testes obtained from patients 15 years of age or older were considered in this study. Unfortunately, in most cases there was little information concerning the gross appearance of the gonads. Microscopically, the organs were studied as to the status of the epithelium in the tubules, the degree of differentiation of the germinal cells and the amount of interstitial tissue.

17. Dr. John Noble, pathologist of the Ancker Hospital, Dr. Nathaniel Lufkin, formerly pathologist of the Minneapolis General Hospital, and Dr. E. T. Bell, of the department of pathology of the University of Minnesota Medical School, gave me access to case histories and specimens of postpubertal ectopic testis in their files.

18. Spangaro, S.: Ueber die histologischen Veränderungen des Hodens, Nebenhodens und Samenleiters von Geburt an bis zum Greisenalter, *Anat. Hefte* 18:599, 1901.

HISTOLOGIC APPEARANCE OF THE DESCENDED TESTIS
AFTER PUBERTY

The adult testis consists of seminiferous tubules separated by a loose interstitium. Lining the tubules are several layers of epithelial cells. The Sertoli or nourishing cells lie directly on the basement membrane of the tubule. They take no part in the spermatogenic cycle. They are elongated, irregularly pyramidal cells with large oval nuclei rich in chromatin. Toward the periphery of the tubule and scattered between the Sertoli cells are the spermatogonia, the progenitors of the adult male sex cells. In the prepubertal testis the Sertoli cells and the spermatogonia are the only cells lining the seminiferous tubules. In the mature testis the spermatogonia are small round elements with nuclei rich in chromatin. By growth the spermatogonia become spermatocytes of the first order. These are large spherical or oval cells. The long axes of the oval cells when the latter are closely packed together are perpendicular to the basement membrane. Each of these cells divides and forms two secondary spermatocytes. The daughter cells of the secondary spermatocytes are called spermatids. The spermatids do not divide but undergo a long series of peculiar transformations before the mature spermatozoa are formed (Blom).

ANALYSIS OF DATA ON UNDESCENDED TESTES

The incidence of undescended testis in the various age groups and the location of the retained gonad in the 46 cases are given in table 1. The histologic findings in this series are recorded in table 2.

In the 46 testes studied, spermatogonia were observed in 17; primary spermatocytes, in 13; secondary spermatocytes, in 8, and spermatids, in 3. In none were spermatozoa seen. It is interesting that spermatids were seen in the undescended testes removed from patients in the third, the fourth and the seventh decades of life. The location of these testes was abdominal, inguinal or near the external ring.

The sooner after puberty the undescended testis is examined, the less degenerated is its histologic appearance. There seems to be no difference in the microscopic picture between the testis retained in the abdomen and that retained in the inguinal canal. In old cryptorchids the tubules begin to atrophy. The tubular epithelium becomes quite degenerated and consists of no more than a hyaline ring in some instances. Occasionally not even Sertoli cells can be differentiated. The amount of interstitial tissue becomes increased and more fibrous with age.

Two cases are of particular interest. In case 21 the patient was a 50 year old man who had a testis retained $\frac{1}{2}$ inch (1.3 cm.) below the external ring. It is possible that this was really a high scrotal testis. It was noted that while about two thirds of the tubules were obliterated by hyaline change, in others the epithelium was fairly normal; in fact.

spermatogenic cells up to primary spermatocytes were seen. In case 43 the patient was a man 60 years old whose ectopic gonad was inguinally retained near the external ring. Microscopically, the tubules showed little atrophy. Spindle-shaped cells similar to spermatids were seen.

However, the finding of so little atrophy of the germinal epithelium in these 2 old cryptorchids seems to be the exception and not the rule. In this study it was present in only 2 of 46 cases (4.4 per cent). Similar

TABLE 1.—*Age Incidence and Location of Undescended Testis in Forty-Six Cases*

Age Incidence		Location of Testis	Side	Cases
Age Group, Yr.	Cases			
15-20	10	Abdominal	Right	9
21-30	12		Left	1
31-40	5		Unknown	2
41-50	7	Inguinal	Right	20
51-60	6		Left	2
61-70	5		Bilateral	2
71-	1	High scrotal or outside external ring (?) (cases 21 and 43).....	Unknown	7
			2
			Perineal.....	1

TABLE 2.—*Histologic Observations in Forty-Six Cases of Postpubertal Undescended Testis*

Age Group, Yr.	Undescended Testes Showing											
	Fairly Normal Tubules	Slightly Atrophic Tubules	Markedly Atrophic Tubules	Sertoli Cells	Spermatogonia	Primary Spermatocytes	Secondary Spermatocytes	Spermatids	Spermatozoa	Slight Increase of Interstitial Tissue	Moderate Increase of Interstitial Tissue	Marked Increase of Interstitial Tissue
15-20	5	4	1	10	8	8	4	4	6	1
21-30	2	4	5	10	5	3	2	1	..	1	4	1
31-40	..	1	4	2	1	1	1	1	..	1
41-50	1	2	6	5	2	1	1	2	1	2
51-60	1	..	3	4	2	1	1	1	..	2
61-70	1	..	3	2	1	2	..
71-	1	1

to the cases in the study by Pace, in which the ectopic testes removed during the fourth and fifth decades of life showed fairly well preserved germinal epithelium, the location of the gonads described in the foregoing paragraph was at or near the external ring. Moore¹⁹ and Southam and Cooper²⁰ concluded that the farther the preadolescent

19. Moore, C. R.: Behavior of Testis Under Varying Experimental Conditions and Function of Scrotum: Transplantation, Cryptorchidism, Vasectomy, Minnesota Med. 7:753, 1924.

20. Southam, A. H., and Cooper, E. R. A.: Hunterian Lecture on the Pathology and Treatment of the Retained Testes in Childhood, Lancet 1:805, 1927.

undescended testis has descended, the more closely it corresponds to the normally located gland at the same age. My findings in old cryptorchids tend to bear out this statement.

CLINICAL STUDIES CONCERNING THE FUNCTIONAL CAPACITY OF THE UNDESCENDED TESTIS

MacCollum and Wangenstein reported the presence of spermatozoa in the semen of bilateral cryptorchids treated by orchiopexy. Patients

TABLE 3.—*Data on Seven Patients with Bilateral Ectopic Testis*

Case and Patient	Age, Yr.	Type of Ectopy	Semen		Treatment and Date	Results of Ejaculation Test After Treatment
			Amount Ejaculated and Date	Spermatozoa		
1 F. F.	30	Bilateral, inguinal	8 cc., 12/21/37	Absent	3,000 units of chorionic gonadotropin; 12/16/38— orchiopexy on left side	2/9/39—no spermatozoa
2 F. W.	20	Bilateral, inguinal	Absent	3,000 units of chorionic gonadotropin	No spermatozoa
3 A. B.	35	Bilateral, abdominal	6 cc.	Absent	3 courses of chorionic gonadotropin, total 15,000 units; also 3 courses of testosterone propionate over eight months, 25 mg. three times per week for eight doses	No results from endocrinotherapy; 8/13/39—no spermatozoa
4 H. T.	22	Bilateral, inguinal	8 cc. 7/23/37	Absent	Course of chorionic gonadotropin and bilateral orchiopexy, treatment ending 9/3/38	1/10/39—spermatozoa present; 4/4/39—spermatozoa present; 8/6/39—spermatozoa present
5 H. R.	19	Bilateral, abdominal (congenital absence of the left testis noted at operation)	11/2/37—orchiopexy on right side; 3/17/38—no left testis found on exploration	5/11/28—no spermatozoa; 10/19/38—no spermatozoa; 3/13/39 no spermatozoa
6 V. H.	19	Bilateral: right, abdominal; left, inguinal	5/5/35	Absent	3,000 units of chorionic gonadotropine; bilateral orchiopexy: 5/2/35—right side; 9/20/35—left side	5/11/37—no spermatozoa; 6/38—no spermatozoa
7 L. O.	22	Bilateral, abdominal	4/27/38	Absent	Bilateral orchiopexy: 4/28/38—left side; 4/18/39—right side	8/28/38—no spermatozoa; 10/23/39—no spermatozoa

showing functional benefits from orchiopexy have been young. Rea has reported the finding of spermatozoa in the semen of 2 patients with bilateral retained testis who had never received any treatment for their anomaly. Since the ages of the treated and the untreated patients whose cases were reported in the literature happened to be about the same, one may wonder whether the treated cryptorchids might not have shown spermatozoa in the semen if they had been followed the same length of time without therapy. I have had the opportunity to study 4 bilateral cryptorchids, 21 to 35 years of age, who refused surgical treatment. One patient had had intermittent endocrinotherapy (table 3, case 3). At the

time of writing these patients have been followed for over two years, and no spermatozoa have been found in their semen. It is my experience that the cryptorchids who at first fail to show spermatozoa in their semen but who later do are those treated by orchiopexy.

For the past few years sperm counts of the ejaculated semen of patients with bilateral cryptorchidism have been made before and after treatment. In 1 of the 7 cases of bilateral ectopy I have studied since Wangenstein's report in 1935, spermatozoa have been seen in the semen after orchiopexy (table 3). This case is reported in detail because, like the case reported by Wangenstein, it presents convincing evidence of the value of orchiopexy in improving the functional capacity of the germinal epithelium of the human undescended testis.

REPORT OF A CASE

The patient when first seen was 21 years old. He had undescended testes inguinally retained and bilateral indirect inguinal hernia. A course of treatment with chorionic gonadotropin (3,000 units over a period of one month) had been given with no appreciable results. On July 23, 1937, orchiopexy was performed on the right side, and a biopsy of the testis was made. On Aug. 19, 1938, orchiopexy was performed on the left side. Biopsy of the right testis showed moderate atrophy of the tubules. Sertoli cells, two or three thick, lined the basement membrane. Except for spermatogonia no specific germinal cells were seen. Biopsies were not made at the time of scrotal thigh detachment, because it was felt that the subsequent size and function of the testis might be jeopardized.

An ejaculation test had been performed before operation, and no spermatozoa were seen. However, subsequent tests on Jan. 10, April 4 and Aug. 6, 1939, revealed occasional spermatozoa in the semen. The number has never been great, but motile forms have been seen. Certainly this patient had signs of potential if not absolute fertility.

TREATMENT OF THE UNDESCENDED TESTIS IN PATIENTS PAST PUBERTY

All surgeons agree that the testis which at puberty has failed to descend spontaneously or by endocrinotherapy should be placed in the scrotum. Up to what age the performance of orchiopexy is justified is an important question. Until about ten years ago it was thought at the University Hospitals that a cosmetic rather than functional result should be expected in patients over 17 years of age with retained testis treated by orchiopexy. Since spermatozoa have been found in the semen of patients 21 and 23 years of age, respectively, with bilateral retained testis treated by scrotal fixation, it has been felt that the indication for orchiopexy could well be extended through the third decade of life in certain cases.

With regard to cryptorchids beyond the third decade of life, one can only rationalize with knowledge in its present status, but the value of orchiopexy seems doubtful. Since in this study less than 5 per cent of the

cryptorchids past puberty showed any degree of preservation of the germinal epithelium and since the older the cryptorchid is, the greater is the testicular degeneration, it is questionable whether a functional result is ever obtained in elderly patients by orchiopexy. Then, too, the desired cosmetic result is not always obtained by scrotal fixation of the retained gland when this is of small size. In my experience the size of the retained testis is a fairly good indicator of what cosmetic and functional results may be expected. For these reasons it is my opinion that an orchidectomy rather than orchiopexy may be indicated for the majority of older cryptorchids. Certainly if there is large associated hernia, if the testis is atrophied, or if one suspects malignant growth, the testis should be removed. Only if the testis is of good size and near the external ring should orchiopexy be considered for these older patients.

SUMMARY

Forty-six retained testes from patients past puberty were available for study. The ages of the patients ranged from 15 to 73 years. Histologically, atrophy, which usually was progressive with age, was observed in all the specimens. Spermatogonia were observed in 17; primary spermatocytes, in 13, secondary spermatocytes, in 8, and spermatids, in 3. In none were spermatozoa seen. Spermatids were seen in undescended testes from persons in the third, fourth and seventh decades of life. The location of these testes was abdominal, inguinal or near the external ring. It is interesting that the germinal epithelium in 2 undescended testes from patients in the sixth and seventh decades of life was fairly well preserved. These testes had been located near the external inguinal ring.

At the University Hospitals patients with bilateral cryptorchidism up to 24 years of age have shown spermatozoa in the semen. For this reason, and because a scrotal position is necessary for continued function of the human testis, it is felt that orchiopexy may well be performed on selected patients with undescended gonads as late as the third decade of life. In older patients, in view of the small size of the testis and the degree of degeneration of the germinal epithelium, it is questionable whether a functional result is obtained by orchiopexy. In this study less than 5 per cent of the cryptorchids past puberty showed any degree of preservation of the germinal epithelium. Only if the testis is of good size and near the external ring should orchiopexy be considered for older cryptorchids.

POSTOPERATIVE INFECTIONS OF THE RESPIRATORY TRACT IN RELATION TO INHALATION AND SPINAL ANESTHESIA

A STUDY OF SIX HUNDRED AND THIRTY-ONE CASES

JOHN LYFORD III, M.D.

BALTIMORE

The purpose of this study was to determine the relative incidence of infections of the respiratory tract after inhalation anesthesia and after spinal anesthesia in patients who had not had preoperative infections of the respiratory tract and who had undergone the same types of abdominal operations.

Since 1901 a copious literature has accumulated concerning postoperative complications involving the respiratory tract. An examination of this literature revealed that there was no previous report comparing the rates of occurrence of such complications in controlled groups of patients who had been subjected to the same abdominal operative procedures under ether, cyclopropane and spinal anesthesia.

MATERIAL AND METHOD

The material consisted of 631 cases in which abdominal operations were performed in the surgical service at Duke Hospital between the years 1930 and 1941. The operations included 245 appendectomies, 216 inguinal herniorrhaphies and 170 operations on the biliary tract, of which 166 were cholecystectomies. The cases in each operative-anesthetic group were consecutive, and in no case was a combination of inhalation and spinal anesthesia employed. The appendectomies were performed through McBurney incisions, and the operations on the biliary tract through incisions in the right rectus muscle.

Included were only those cases in which it could be determined definitely from the record that no infection of the respiratory tract existed at the time of operation. Postoperative infections of the respiratory tract were considered to have occurred only when the patients showed definite acute infections of the upper respiratory tract or pulmonary signs on physical or roentgen examination as recorded in the postoperative progress notes. The postoperative infections of the respiratory tract were classified as: (a) pneumonia and (b) nonpneumonic acute infections of the respiratory tract, e. g. acute bronchitis or coryza. The numerous subtables were omitted from this report in order to avoid confusion from an excess of charts and because they did not add materially to the study. All tables and calculations were checked by the chi square test.

From the Department of Surgery, Duke University School of Medicine and Duke Hospital, Durham, N. C.

INCIDENCE OF POSTOPERATIVE INFECTIONS OF THE
RESPIRATORY TRACT

In this study it was found that in patients who did not have any infection of the respiratory tract at the time of operation the incidence of postoperative infections of the respiratory tract was: after ether anesthesia 5.8 per cent, after cyclopropane anesthesia 4.9 per cent and after spinal anesthesia 7.5 per cent (table 1). That is, approximately the same proportion of patients had postoperative infections of the respiratory tract irrespective of the type of anesthesia used. Although these figures are probably small enough to make it not too markedly significant, it should be observed that the incidence after spinal anes-

TABLE 1.—*Postoperative Infections of the Respiratory Tract in Relation to the Type of Anesthesia*

	Ether			Cyclo- propane *		Spinal			Totals		
	Appendectomies	Herniorrhaphies	Biliary Tract	Appendectomies	Herniorrhaphies	Appendectomies	Herniorrhaphies	Biliary Tract	Ether	Cyclopropane	Spinal
Total number of patients.....	80	73	89	87	76	78	67	81	242	163	226
Patients with postoperative infections of the respiratory tract.....	5	4	5	5	3	6	5	6	14	8	17
Percentage of patients with postoperative infections †.....	6.3%	5.5%	5.6%	5.8%	3.9%	7.7%	7.5%	7.4%	5.8%	4.9%	7.5%

* Too few operations on the biliary tract were performed under cyclopropane to be included in this study.
† This is expressed as per cent of the total number of patients in the operative-anesthetic group.

thetia was 35 per cent greater than that after cyclopropane anesthesia and 23 per cent greater than that after ether anesthesia. These same relative proportions between the types of anesthesia held in each operative-anesthetic group (table 1). There were no deaths in this series of cases.

In the literature the incidence of postoperative respiratory tract complications has been reported as varying between 1.04 per cent and 21 per cent with ether,¹ between 0 per cent and 2.07 per cent with cyclo-

1. (a) Gray, H. K.: Postoperative Pulmonary Complications and Postoperative Use of Trendelenburg Position, *Minnesota Med.* **18**:273 (May) 1935. (b) King, D. S.: Postoperative Pulmonary Complications: Statistical Study Based on Two Years' Personal Observation, *Surg., Gynec. & Obst.* **56**:43 (Jan.) 1933. (c) Ryan, T. J.: Hyperventilation in Abdominal Surgery, *J. A. M. A.* **107**:267 (July 25) 1936. (d) Sise, L. F.: Postoperative Pulmonary Complications: Comparison of Effect of Spinal and Ether Anesthesia, *S. Clin. North*

propane,² and between 2 per cent and 12.5 per cent with spinal anesthesia.³ Brown and Debenham⁴ reported the incidence of postoperative pulmonary complications in 63 cases in which abdominal operations were performed as 4.8 per cent with ether anesthesia and 12.5 per cent with spinal anesthesia. They stated also that in 812 cases in which operations of various kinds were performed pulmonary complications were four and twenty-nine hundredths times more frequent after spinal than after inhalation anesthesia despite the fact that the "bad risks" were done with the patients under inhalation anesthesia. Brown⁵ reported in his series that the incidence of pulmonary atelectasis was greater after spinal than after any form of inhalation anesthesia. The literature contains several reports of the incidence of postoperative respiratory tract complications as being at least as great after spinal as after inhalation anesthesia.⁶

America **12**:649 (June) 1932. (e) Whipple, A. O.: A Study of Postoperative Pneumonitis, Surg., Gynec. & Obst. **26**:29 (Jan.) 1918. (f) Wiggin, S. C.: Present Status of Ether Anesthesia, Anesth. & Analg. **15**:105 (May-June) 1936.

2. Bogan, J. B.: Clinical Evaluation of Cyclopropane After Its Use in Three Hundred Surgical Anesthesias, Anesth. & Analg. **15**:275 (Nov.-Dec.) 1936. Burford, G. E.: Pulmonary Complications Following 1,333 Administrations of Cyclopropane, J. A. M. A. **110**:1087 (April 2) 1938. Moffitt, J. A., and Mechling, G. S.: Comparison of Cyclopropane with Other Anesthetics, Anesth. & Analg. **15**:225 (Sept.-Oct.) 1936. Taylor, I. B.; Bennett, J. H., and Waters, R. M.: Anesthesia at Wisconsin General Hospital: Three Year Statistical Report; Anesthetic Methods and Postoperative Respiratory Complications, *ibid.* **16**:198 (July-Aug.) 1937.

3. King, O. C.: Spinal Analgesia: Report of Fifteen Hundred Cases, Ann. Surg. **101**:690 (Feb.) 1935. Moore, F. R.: Report of 2,434 Spinal Anesthesias, with Special Reference to Postoperative Pulmonary Complications in One Thousand Cases, U. S. Nav. M. Bull. **31**:160 (April) 1933. Washburn, F. H.: What We Have Learned from Five Hundred Spinal Anesthesias, New England J. Med. **209**:345 (Aug. 17) 1933. Sise.^{1d}

4. Brown, A. L., and Debenham, M. W.: Postoperative Pulmonary Complications: Study of Their Relative Incidence Following Inhalation Anesthesia and Spinal Anesthesia, J. A. M. A. **99**:209 (July 16) 1932.

5. Brown, A. L.: Postoperative Pulmonary Atelectasis: Observation on Importance of Different Types of Bronchial Secretions and Anesthesia, Arch. Surg. **22**:976 (June) 1931.

6. Arnheim, E. E., and Mage, S.: Spinal Anesthesia: Analysis of Four Hundred and Ninety-Seven Cases, Ann. Surg. **93**:929 (April) 1931. Emmett, J. M.: Fourteen Hundred and Fifteen Spinal Anesthesias with Special Reference to Indications, Complications, and Mortality—with Cases Reported and Charts, Virginia M. Monthly **62**:304 (Sept.) 1935. Foss, H. L., and Schwalm, L. J.: Relative Merits of Spinal and Ether Anesthesia, J. A. M. A. **101**:1711 (Nov. 25) 1933. Houston, J. C.: Comparison of Ether, Spinal, and Cyclopropane Anesthesia, Canad. M. A. J. **40**:143 (Feb.) 1939. McKittrick, L. S.; McClure, W. L., and Sweet, R. H.: Spinal Anesthesia in Abdominal Surgery, Surg., Gynec. & Obst. **52**:898 (April) 1931. Stabins, S. J., and Morton, J. J.: Observations on Spinal Anesthesia, Ann. Surg. **91**:242 (Feb.) 1930.

FACTORS NOT INFLUENCING THE INCIDENCE OF POSTOPERATIVE INFECTIONS OF THE RESPIRATORY TRACT

Age.—In each anesthetic-age group there was an average distribution of cases (table 2). In the anesthetic groups there was no regularity in the incidence of postoperative infections of the respiratory tract (table 3), and hence the incidence could not be shown to be affected by the age of the patients. Fuller⁷ reported similar findings in his study. Cleveland⁸ stated that in his series 52 per cent of the post-

TABLE 2.—*Age Distribution of Patients**

	Ether (242 Cases)		Cyclopropane (163 Cases)		Spinal (226 Cases)	
	Patients	Per Cent	Patients	Per Cent	Patients	Per Cent
0-9 years.....	32	13.3	2	1.3	0	0.0
10-19 years.....	49	20.3	48	29.4	17	7.6
20-29 years.....	61	25.3	60	36.8	60	26.5
30-39 years.....	31	12.7	23	14.1	53	23.4
40-49 years.....	38	15.7	12	7.3	53	23.4
50 years and over.....	31	12.7	18	11.1	43	19.1

* This is expressed as per cent of the total number of patients in the anesthetic group.

TABLE 3.—*Relation Between Postoperative Infections of the Respiratory Tract and Age of Patients Studied**

	Ether (14 Cases)		Cyclopropane (8 Cases)		Spinal (17 Cases)	
	Patients	Per Cent	Patients	Per Cent	Patients	Per Cent
0-9 years.....	2	14.3	0	0.0	0	0.0
10-19 years.....	1	7.1	2	25.0	2	11.8
20-29 years.....	4	28.6	3	37.5	1	5.8
30-39 years.....	2	14.3	2	25.0	2	11.8
40-49 years.....	2	14.3	0	0.0	8	47.1
50 years and over.....	3	21.4	1	12.5	4	23.5

* This is expressed as per cent of the total number of patients with postoperative infections of the respiratory tract in each anesthetic group.

operative respiratory tract complications occurred in patients who were in the third and fourth decades of life. The present study revealed that a similar figure held for combinations of several other decades (table 3).

Duration of the Operative-Anesthetic Time.—Rovenstine and Taylor⁹ reported that the duration of the operation was the most important

7. Fuller, C. J.: Analysis of Postoperative Pulmonary Complications Based on Cases at University College Hospital, London, in One Year, *Lancet* **1:115** (Jan. 18) 1930.

8. Cleveland, M.: Further Studies in Postoperative Pneumonitis, *Surg., Gynec. & Obst.* **28:282** (March) 1919.

9. Rovenstine, E. A., and Taylor, I. B.: Postoperative Respiratory Complications: Occurrence Following 7,874 Anesthesias, *Am. J. M. Sc.* **191:807** (June) 1936.

factor in the development of postoperative respiratory tract complications. Fuller⁷ found the duration of the operation not to be a factor in the incidence of postoperative infections of the respiratory tract. In the present 631 cases the incidence with each type of anesthesia varied relatively little between the different operative procedures, i. e. between the short (appendectomies), intermediate (herniorrhaphies) and relatively long (operations on the biliary tract) operative-anesthetic procedures (table 1).

Sex.—In this series sex could not be shown to be a factor contributing to the occurrence of postoperative infections of the respiratory tract. The incidence was not markedly greater in either sex (table 4), although it was slightly higher in females than in males in each anesthetic group. Cleveland⁸ and D. King^{1b} reported the incidence in their studies respectively as four times and twice as great in men as in women.

TABLE 4.—*Relation Between Postoperative Infections of the Respiratory Tract and Sex of Patients Studied**

	Ether		Cyclopropane		Spinal	
	Male	Female	Male	Female	Male	Female
Total number of patients.....	142	100	130	33	122	104
Patients with postoperative infections of the respiratory tract.....	8	6	6	2	9	8
Per cent of patients with postoperative infections.....	5.6%	6.0%	4.6%	6.1%	7.3%	7.7%

* This is expressed as per cent of the total number of patients in each anesthetic-sex group.

Preoperative Complications.—The preoperative complications were considered to be those usually accepted as making the patient a possible "bad risk"—e. g., diseases of the cardiovascular system or kidneys, diabetes mellitus, peritonitis or cachexia. Of the patients with such preoperative complications the proportion in which postoperative infections of the respiratory tract developed was essentially the same in each anesthetic group; i. e., the incidence was with ether anesthesia 7.1 per cent, with cyclopropane anesthesia 7.7 per cent and with spinal anesthesia 10 per cent. Likewise, the proportion of patients with postoperative infections of the respiratory tract who had preoperative complications was not markedly greatest with any one of the three types of anesthesia: ether, 14.3 per cent; cyclopropane, 12.5 per cent; spinal, 17.6 per cent. Hence, preoperative complications were not a significant factor contributing to the incidence of postoperative respiratory tract complications.

The Kind of Spinal Anesthetic Agent and the Preoperative Medication.—The choice and the amount of spinal anesthetic agent had no effect on the incidence of postoperative infections of the respiratory tract. The incidence was relatively the same in the group of patients receiv-

ing procaine hydrochloride alone as in the group given both procaine hydrochloride and pontocaine hydrochloride. The dosage of the drugs was not a factor, since in each operative-spinal anesthetic group the patients received approximately the same amount of drug. Nor did the preanesthetic medication affect the incidence, since all 631 patients received essentially the same medication.

Blood Pressure Changes.—No estimate of the relationship between the incidence of postoperative infections of the respiratory tract and changes in blood pressure during the operation could be made in this study because it was not routine to record the blood pressure of patients given inhalation anesthesia. But when spinal anesthesia was used, the blood pressure was recorded routinely at regular intervals during the operation, and in these cases there was no correlation between changes in the blood pressure during the anesthesia and the incidence of infections of the respiratory tract postoperatively.

From the data available no explanation can be given as to the anatomic-physiologic cause of postoperative infections of the respiratory tract. Whipple¹⁰ suggested as predisposing factors pulmonary congestion and the inhibition of normal respiratory movements resulting from the abdominal incision. Czerny¹⁰ emphasized the role of pain in the abdominal wound as a factor in preventing sufficient aeration of the lungs and expectoration of mucus from the trachea.

SUMMARY

Six-hundred and thirty-one cases in which abdominal operations were performed under ether, cyclopropane or spinal anesthesia on patients without infections of the respiratory tract at the time of operation have been reviewed to determine the incidence of postoperative infections of the respiratory tract with each type of anesthesia. In this study certain findings appeared significant:

1. Approximately the same proportion of patients without infections of the respiratory tract at the time of operation acquired postoperative infections of the respiratory tract with inhalation and with spinal anesthesia; i. e., the incidence was with ether anesthesia 5.8 per cent, with cyclopropane anesthesia 4.9 per cent and with spinal anesthesia 7.5 per cent.

2. The incidence of postoperative infections of the respiratory tract was unaffected by the age or the sex of the patients, the length of the operative-anesthetic time, the preoperative complications, the kind or the amount of the spinal anesthetic agent, the preanesthetic medication or the blood pressure changes during the anesthesia.

10. Czerny, cited by Henle: Ueber Pneumonie und Laparotomie, Arch. f. klin. Chir. 64:339, 1901.

PREOPERATIVE AND POSTOPERATIVE INFECTIONS OF THE RESPIRATORY TRACT IN RELATION TO INHALATION AND SPINAL ANESTHESIA

JOHN LYFORD III, M.D.

BALTIMORE

In the preceding article¹ are reported the relative rates of occurrence of infections of the respiratory tract after ether, cyclopropane and spinal anesthesia in patients who did not have any infections of the respiratory tract at the time of operation. An examination of the literature had shown no previous report comparing the rates of incidence of preoperative and postoperative infections of the respiratory tract in relation to inhalation and spinal anesthesia. The purpose of the present study was to determine the relative incidence of acute infections of the respiratory tract after ether, cyclopropane and spinal anesthesia in patients who had been shown to have the kind of low grade, chronic preoperative infections of the respiratory tract not generally considered by surgeons to be contraindications to even elective operations.

MATERIAL AND METHOD

The material was limited to 120 cases in which abdominal operations, including appendectomies, inguinal herniorrhaphies and cholecystectomies, were performed on patients who were under the three types of anesthesia and who had been shown to have such chronic preoperative infections of the respiratory tract. The operations were performed during a ten year period, and the cases in each operative-anesthetic group were consecutive. In no case were combinations of any two of the three types of anesthesia employed.

The criteria followed in determining the existence of a low grade, chronic preoperative infection of the respiratory tract necessitated finding described in the patient's preoperative record: (a) exudate and injection of the tonsils, (b) chronic postnasal discharge or (c) pulmonary rales characterized as being associated with chronic bronchitis. Postoperative infection of the respiratory tract was considered to have occurred only when the patient had definite pneumonia, acute bronchitis or acute coryza, determined by physical or roentgen examination, as recorded in the postoperative progress notes.

In this study the decade of life of the patient at the time of operation, the type of abdominal operative procedure and the criteria for the postoperative infection of the respiratory tract were the same as in the previous study.¹

From the Department of Surgery, Duke University School of Medicine and Duke Hospital, Durham, N. C.

1. Lyford, J., III: Postoperative Infections of the Respiratory Tract in Relation to Inhalation and Spinal Anesthesia: A Study of Six Hundred and Thirty-One Cases, Arch. Surg., this issue, p. 35.

COMMENT

It was found in this group of patients having low grade, chronic preoperative infections of the respiratory tract that the incidence of acute postoperative infections of the respiratory tract was approximately two and one-half times as great after spinal as after inhalation anesthesia (table). Analysis of the anesthetic groups revealed that 39.5 per cent of the patients with chronic preoperative infections of the respiratory tract operated on under spinal anesthesia had acute postoperative involvement of the respiratory tract, as opposed to 13.5 per cent of those under ether anesthesia and 17.5 per cent of those under cyclopropane anesthesia (table).

The results were checked for statistical significance by the chi square test. The value of such tests was well discussed by Campbell.² In the present study it was found that the variation between the incidence of infections of the respiratory tract after spinal anesthesia and that after

Incidence of Postoperative Infections of the Respiratory Tract in Patients Having Low Grade, Chronic Preoperative Infections of the Respiratory Tract

	Ether	Cyclopropane	Spinal
Total number of patients.....	37	40	43
Patients with postoperative infections of the respiratory tract	5	7	17
Per cent of patients with postoperative infections*.....	13.5%	17.5%	39.5%

* This is expressed as per cent of the total number of patients in the anesthetic group.

ether anesthesia, as well as after spinal and after cyclopropane anesthesia, was markedly significant since there was approximately only 1 chance in 25 that the results stated would be altered significantly by increasing the number of cases in each anesthetic group. The relative occurrence of infections of the respiratory tract after ether and cyclopropane anesthesia did not vary widely enough to be statistically significant.

King³ stated that his studies showed preoperative infections of the respiratory tract to have a minor role in the development of postoperative respiratory tract complications since only 18.7 per cent of his patients with postoperative respiratory tract complications had preoperative infections of the upper respiratory tract. In a previous study¹ it was found that in a group of patients without any infections of the respiratory tract at the time of operation the incidence of acute postoperative infections of the respiratory tract was 5.8 per cent after ether, 4.9 per cent after cyclopropane and 7.5 per cent after spinal anesthesia. The markedly increased incidence of infections of the respiratory tract after all three

2. Campbell, H. E.: The Statistical Method, Surgery 9:825 (June) 1941.

3. King, D. S.: Postoperative Pulmonary Complications: Statistical Study Based on Two Years' Personal Observation, Surg., Gynec. & Obst. 56:43 (Jan.) 1933.

types of anesthesia in the present group of patients having low grade, chronic preoperative infections of the respiratory tract suggests that low grade preoperative infections of the respiratory tract were of major importance in the development of the postoperative involvements of the respiratory tract, especially after spinal anesthesia. Whipple⁴ offered as a factor predisposing to postoperative pulmonary involvement the presence of a preoperative infection of the respiratory tract.

In another series¹ it was shown that the incidence of postoperative infections of the respiratory tract was unaffected by the age or the sex of the patients, the length of the operative-anesthetic time, preoperative complications other than infections of the respiratory tract, the kind or the amount of the spinal anesthetic agent, the preanesthetic medication or the blood pressure changes during the anesthesia. The same methods of analysis applied to the present group of cases indicated that these factors did not significantly affect the incidence of postoperative infections of the respiratory tract in these patients with low grade, chronic preoperative infections of the respiratory tract.

SUMMARY

One hundred and twenty cases in which abdominal operations were performed on patients who were under ether, cyclopropane or spinal anesthesia and who had been shown to have low grade, chronic preoperative infections of the respiratory tract of the kind not generally considered contraindications to even elective operations have been analyzed to determine the relative incidence of acute postoperative infections of the respiratory tract after each type of anesthesia.

Patients having low grade, chronic preoperative infections of the respiratory tract had acute postoperative infections of this tract approximately two and one-half times as frequently after spinal as after inhalation anesthesia; i. e., the incidence was after ether anesthesia 13.5 per cent, after cyclopropane anesthesia 17.5 per cent and after spinal anesthesia 39.5 per cent.

The incidence of acute postoperative infections of the respiratory tract after each type of anesthesia in patients with low grade, chronic preoperative infections of this tract was found to be markedly greater than the incidence in a previous series of patients who had not had any preoperative infections of the respiratory tract. This finding suggests that the presence of low grade preoperative infections of the respiratory tract of the kind not generally considered contraindications to even elective operations is of sufficient significance as a factor in the development of acute postoperative infections of the respiratory tract to warrant further analysis as to the choice of anesthesia.

4. Whipple, A. O.: A Study of Postoperative Pneumonitis, Surg., Gynec. & Obst. 26:29 (Jan.) 1918.

PRIMARY SUTURE OF THE COMMON BILE DUCT IN CHOLEDOCHOLITHIASIS

P. L. MIRIZZI, M.D.

CÓRDOBA, ARGENTINA

Primary suture of the common bile duct, also called immediate choledochorrhaphy, consists of making a perfect suture of the surgical incision of the duct after having completely removed the intracholedochal concretions and after having verified the patency of the papilla of Vater.

A normal elimination of bile through the papilla of Vater with complete absence of stagnation for the first two weeks after operation is the most important requisite for healing of the incision by first intention (Walzel¹), but this depends on patency of the papilla of Vater and on free elimination of bile after removal of the concretions. According to modern criteria, the thickness of the wall of the duct, the dilatation of the ductal lumen, the turbid aspect of the bile and the presence of gravel in the choledochal bile, as well as other minor alterations, are factors of secondary importance (Wegłowski²) in healing of the incised common bile duct by first intention. Opinions which attributed primary importance to these alterations prevailed in the past, when primary suture of the common bile duct was done only in exceptionally rare cases. The few surgeons who found many indications for primary suture reported choleperitoneum as a frequent complication (Bernhard³) and advised against the operation.

Von Eiselsberg⁴ and his school advised primary suture of the common bile duct, provided a drain was placed through the ampulla of Vater after dilation of Vater's papilla (Walzel). The procedure was approved by well known surgeons because of its simple technic and laudable aim (Duval⁵). I have used Duval's simple modification of the procedure only in cases in which the prognosis was favorable, namely,

1. Walzel, P.: Zur Therapie des Choledochussteiner, Arch. f. klin. Chir. **126**: 320, 1933.

2. Wegłowski, R.: Les interventions opératoires sur le cholédoque, Presse méd. **34**:1124, 1926.

3. Bernhard, F.: Die Bedeutung der Cholangiographie für Praxis und Forschung, Chirurg **9**:201, 1937; Der Dauererfolg zweizeitiger Operationen an den Gallenwegen, Beitr. z. klin. Chir. **169**:25, 1939.

4. Von Eiselsberg, cited by Walzel.¹

5. Duval, P.: Abandon du drainage biliaire externe dans la cholédochotomie pour le drainage duodénal transvatrien par tube perdu, Bull. et mém. Soc. nat. de chir. **50**:755, 1924.

in those cases in which jaundice had recently appeared, in which there were no clinical symptoms of sepsis and in which the general condition of the patient was good (Duval and Richard⁶). Dilation of the papilla was difficult in some cases and impossible in others; in a third group, in which the patients were operated on under control of cholangiography, I observed regurgitation of the injected iodized poppyseed oil to Vater's duct in the first few hours after a drain was placed through the ampulla of Vater, and jaundice in the days which followed. The results showed the inadvisability of transvaterian drainage. The reflux of bile to the pancreatic duct causes some inconvenience. It is not the predominant pathogenic factor of necrotic acute pancreopathy, but clinical studies and vivisection have shown that it is important. A drain placed in Vater's ampulla probably acts like a foreign body or an impacted calculus and induces spasm of Oddi's sphincter with spasmodic predominance in the sympathicotropic lower portion of the ampulla. Dilation of Vater's papilla, on the other hand, may cause trauma to the pancreas, such as that caused by violent maneuvers used in removing calculi or impacted concretions from the terminal portion of the common bile duct. Certain conditions may result from local trauma which are propitious for the development of postoperative complications, such as pancreatic necrosis and biliary peritonitis. The aforementioned considerations prove the inadvisability of transvaterian drainage; in this connection the lack of further reports and statistics in the literature is itself significant.

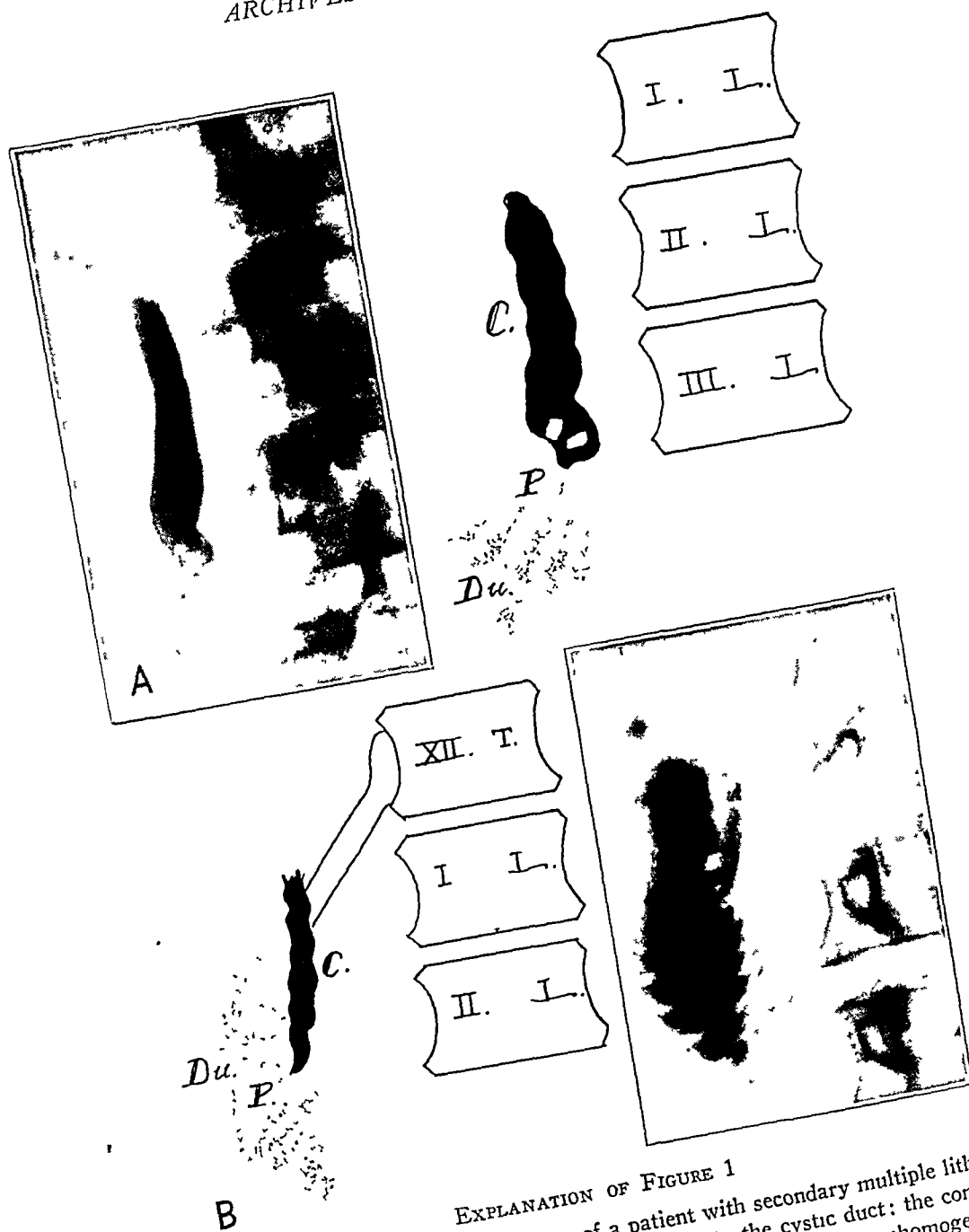
In the past the unsatisfactory results from primary suture of the common bile duct were due to the lack of proper methods for examining the patency of Vater's papilla and for determining whether all the intraductal calculi had been removed. In cases in which any of the mentioned requirements were wanting, primary suture of the common bile duct was frequently complicated by dehiscence of the incision of the common bile duct with consequent development of choleperitoneum.

INDISPENSABLE REQUIREMENTS

For primary suture of the common bile duct, the following requirements are important: (1) patency of Vater's papilla; (2) complete removal of all intraductal calculi; (3) a normal pancreas, and (4) a perfect suture of the duct.

Patency of Vater's Papilla.—The degree of patency of Vater's papilla is properly evaluated during operation by cholangiography, which actually shows whether or not there is that free course of bile to the duodenum (fig. 1) which is indispensable when primary suture of the duct is to be used. Operative cholangiography gives the same feeling of

6. Duval, P., and Richard, A.: Le drainage duodénal transvaterien par tube perdu dans la cholédochotomie, *J. de chir.* 26:129, 1925.



EXPLANATION OF FIGURE 1

Fig. 1.—A, operative cholangiogram of a patient with secondary multiple lithiasis of the common bile duct. Iodized oil was injected into the cystic duct: the common bile duct (C) was somewhat dilated and uniformly injected; the nonhomogeneous portion at the lower end of the duct above the papilla (P) contained two small faceted calculi; some of the iodized oil passed to the duodenum (Du). B, operative cholangiogram of a patient with solitary calculus of the papilla. A concretion the size of a large pea was removed from the papilla; after this a few cubic centimeters of iodized oil was injected into the cystic duct. The lumen of the common bile duct became diminished in diameter, and the iodized oil drained freely from the duct to the duodenum. T and L signify thoracic and lumbar, respectively.

safety before primary suture of the common bile duct as it does before closure of the operative wound without drainage after cholecystectomy. The ideal cholecystectomy was discredited because of the belief that the ligation of the cystic duct might loosen with consequent development of choleperitoneum. That this is a mistaken idea was proved in my personal practice by the use of operative cholangiography in a series of 350 instances in which the wound was closed without drainage. The results revindicate the surgical tactics and the bases from which the technic was developed. The same phenomenon of revindication will be seen to apply to primary suture of the common bile duct by those who may be in doubt as to the value of the technic.

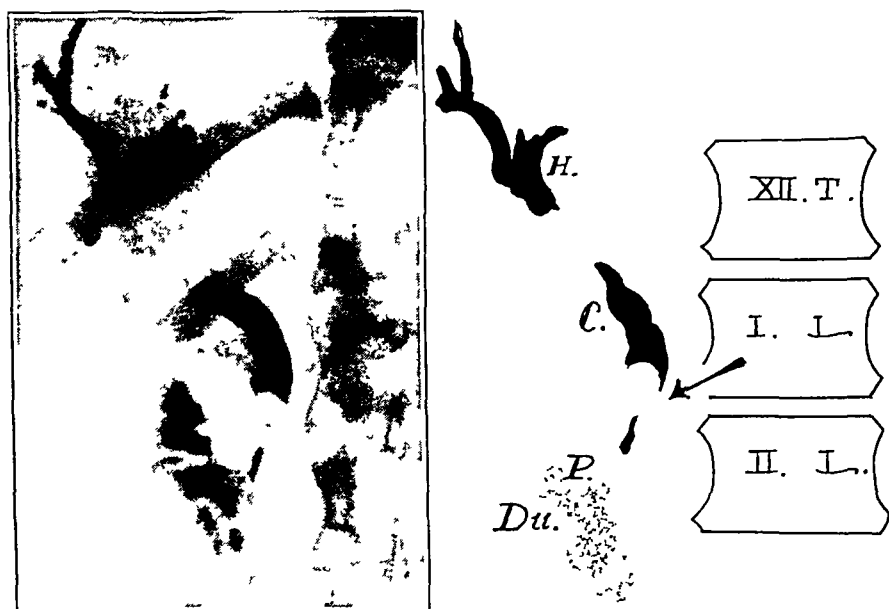


Fig. 2—Operative cholangiogram of a patient with solitary lithiasis of the common bile duct and stenosing pancreatitis. Iodized oil (3 cc.) was injected through the cystic duct. The biliary tree was enlarged in diameter. The system of the hepatic duct (*H*) was rendered opaque. At the level of the arrow the image of the punched hollow in the common bile duct is characteristic of calculus. Some iodized oil passed through the papilla to the duodenum.

Now, primary suture of the common bile duct may be done by way of exception in the presence of a relative obstacle to the elimination of bile, provided derivation of bile is certainly feasible.

In some cases, the common bile duct, with a thin and elastic wall, contains small faceted concretions, and after these have been entirely removed, the distal portion of the duct shows a stricture at the level of the pancreas (fig. 2), or else there is delayed passage of the opaque

substance to the duodenum because of resistance of Vater's papilla. In cases of this type, if the valvular system and the caliber of the cystic duct are normal, the primary suture of the common bile duct may be complemented with a cysticoduodenostomy. This associated operation has been used under these conditions without inconvenience in 5 cases (Olmedo⁷).

Removal of Intraductal Calculi.—Total removal of the calculi from the common bile duct is easy when there is only one calculus, whereas it is difficult in the presence of many concretions. Since complete removal of the ductal concretions is necessary for primary suture of the duct, an examination of the duct is made during operation by cholangiography, which is reliable.

Normal Pancreas.—An indispensable condition to obviating external drainage is the avoidance of any possible trauma to the pancreas during operation. Caution is especially directed to the removal of calculi from the papilla of Vater and also to the removal of concretions lodged in the transpancreatic segment of the common bile duct. Violent maneuvers necessarily traumatize the pancreas with consequent development of necrosis to a greater or lesser extent in zones of the tissue. If the calculus is removed during the first maneuvers and without violence, external drainage can be avoided. If choledochotomy is difficult, the head of the pancreas is more or less traumatized; in such a case it is advisable to employ Kehr's operation.

Perfect Suture of the Duct.—Perfect suture of the common bile duct can be made when the anatomic condition of the duct is good and the proper instruments are used. In cases in which the common bile duct is papyraceous, it is advisable to make incisions no larger than necessary to allow removal of the small concretion. All laceration during the maneuvers must be avoided. As a principle, suture is proscribed when coaptation of the borders of the incision is not perfect and closure of the incision is not hermetic. The subhepatic space is always drained.

TECHNIC

The technic is based on the physiology of the hepatic duct, the integrity of which is spared during the operation. The procedure consists in supraduodenal transverse choledochotomy. Whether the operation is performed on a common bile duct with an elastic wall and a normal aspect or on a duct with a thickened wall and a dilated lumen, two loops of fine thread are used on the anterior aspect of the duct 1 cm. apart. An appropriately curved needle is used. The loops are made immediately above the duodenum along the axis of the duct. Light

7. Olmedo, F. A.: Personal communication to the author.

traction makes the anterior wall of the duct accessible to a bent bistoury, the point of which makes a transverse incision between the two loops. The incision is enlarged according to the diameter of the calculus by pushing the anterior wall of the common bile duct outward, either to the right or to the left (fig. 3). While the incision is being made, the sharp edge of the bistoury is pointed up. A small incision is generally sufficient in operations on ducts of elastic walls with small concretions. After the calculi are removed, the common bile duct is sutured with a continuous suture of no. 00 catgut. The ideal suture is that in which the stitches do not perforate; this gives a hermetic closure of

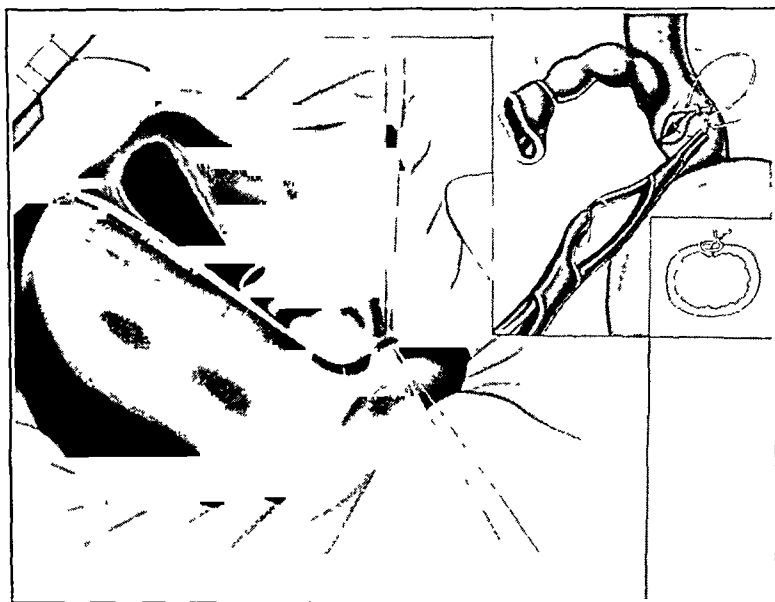


Fig. 3.—Transverse choledochotomy. The anterior wall of the common bile duct is elevated by means of two loops of thread; a transverse incision is made with a bent bistoury, and outward traction of the anterior wall of the duct is performed by means of the instrument's sharp edge and point (transfixion). The inset shows continued suture of the anterior wall of the common bile duct with nonperforating stitches.

the duct. It can generally be accomplished if the wall of the duct is thick.

As a rule, the injection of an opaque substance for examination of the route of bile elimination is made through the cystic duct, which has previously been left open for that purpose. When the cystic route cannot be used, the injection is made directly through the common bile duct just before the last stitch is taken.

OBJECTIONS

The principal objections to the procedure are the development of infection of the biliary tract and of choleperitoneum.

It is stated that the bile should be drained to prevent infection of the biliary tract. However, a simple review of the bacteriologic verifications by Elkeles⁸ proves that the statement is unjustified. Infection of the biliary tract develops and evolves as long as concretions are present and stagnation of the bile obtains. The most efficient manner of controlling infection is to remove the calculi and establish a free course of the bile to the intestine. I believe that primary suture of the common bile duct has more extensive indications than those given by its advocates (Steindl⁹). Infection of the biliary tract is not a contra-indication (Kirschner¹⁰).

In the study of the biliary apparatus, as carried on up to now in the laboratories of the Medical School of Córdoba, either bile taken from the gallbladder during operation or the wall of the gallbladder was sent to the laboratory immediately after operation for bacteriologic study. Among the many investigations, the researches showing the role of the wall of the gallbladder in the development of infection of the biliary tract are of great importance. The colon bacillus and the streptococcus are the primary causal agents in the development of the infection, which evolves in the presence of various bacteria of secondary pathogenic importance.

The frequent involvement of the main route of elimination of bile in the course of cholecystitis (as verified by operative cholangiography) and the lack of bacteriologic studies of the bile of the hepatic and common bile ducts showed the need of research on the subject (Elkeles).

Observations have been made in 108 cases. In 51 cases, in addition to the bile of the gallbladder, the wall of the structure and the cystic ganglion (the material commonly obtained), the bile of the common bile duct and the contents of the duodenum also were secured. Some or all of these items in 50 cases yielded, on culture, pathogenic bacteria of given types, namely, of the colon bacillus, streptococcic, typhoid and proteus groups. These bacteria were the active agents in the production of the inflammation.

In 6 of 9 cases of supposed empyema the bile of the gallbladder was sterile; on the other hand, the gallbladder wall contained bacteria.

In 3 cases of cholecystitis the cultures made of the bile and the wall of the gallbladder, the duodenal fluid and the bile of the common bile

8. Elkeles, G.: Personal communication to the author.

9. Steindl, H.: *Chirurgie der Gallenwege und dazugehörige Stoffwechselprobleme*, Wien. klin. Wchnschr. **51**:920, 1938.

10. Kirschner, M., in discussion on Bernhard, F.: *Ueber neuere Gesichtspunkte aus der Chirurgie der Gallenwege*, Arch. f. klin. Chir. **189**:79, 1937.

duct showed colonies of typhoid bacilli. The presence of *Eberthella typhi* in the cultures, notwithstanding that the main route of elimination was normal, could be explained as a consequence of the fact that bile is favorable to the growth of *Eberthella*.

In 12 of 15 cases of calculous chronic cholecystitis the bile from the common bile duct was sterile although there were foci of infection in the neighborhood. In these 12 cases the main route of elimination of bile was free from any anatomic or functional obstacle, and the condition followed a clinical course without fever. In the remaining 3 cases in the group the choledochal bile when cultured gave scanty colonies, which seemed to be still more scanty when compared with the abundant colonies grown from material taken from other parts of the biliary tract.

The results obtained with the bile of the common bile duct in 19 cases of choledochal lithiasis are interesting. The bile of the duct was infected in 16 cases. It was sterile and of normal aspect in the 3 remaining cases in the group. The common bile duct had a thin wall and a lumen slightly increased in diameter. It was in active peristalsis. Everything seemed to indicate that the calculi had immigrated into the duct shortly before the operation.

In 9 cases in which the system of the common bile ducts did not contain calculi, the bile of the common bile duct was sterile, notwithstanding that the bile and the wall of the gallbladder and the duodenal liquid contained pathogenic bacteria. Stenosing inflammation of the sphincter of Oddi was present in 2 cases of the group, and dyskinesia (dystonia), in the other 2 cases.

Among cases recently observed, there were 2 instances of cholangiopathy without any concretions. In the first, the gallbladder was sclerotic and atrophic, the cystic duct was well preserved, stenosing pancreatitis without evident jaundice was present, and the bile of the common bile duct revealed a scanty number of bacterial colonies, though there was a great development of colonies in cultures of material from the biliary tract other than choledochal bile. In the second instance, the gallbladder was sclerotic and atrophic; it was in open communication with the main route of elimination of bile, and there was obstructive pancreatitis with an icteric syndrome of two months' duration. In this case the bile of the common duct was rich in pathogenic bacteria.

PRACTICAL DEDUCTIONS

The researches on the bacteriology of the biliary tract and of the duodenum together with the studies of the anatomic and the functional conditions of the main route of elimination of bile seem to indicate that

bile of the common duct has a great capacity for keeping free of bacteria. The observations seem to indicate that stagnation of bile due to dyskinesia and inflammation of the sphincter of Oddi is insufficient in itself to cause infection of the common bile duct. As a rule, if the concretions are allowed to remain in the common bile duct and injure its wall, calculus of the common bile duct leads to angiocholitis. Stenosing pancreatitis develops in the same manner, and the more complete the obstruction, the more acute the condition.

It is logical to suppose that the main route of bile elimination will regain its natural sterility immediately after the concretions of the hepatic and common bile ducts are removed and the mechanical factors which obstruct the free elimination of bile are eliminated. These are the fundamental considerations which justify primary suture of the common bile duct.

The common bile duct has defensive properties which make it more resistant than the other structures of the biliary tract. It has been found by vivisection to stand the action of pancreatic extracts and of colon bacilli better than the gallbladder; in fact, while the latter shows necrosis from these influences, the duct is not injured if the stagnation of the bile is suppressed in time (Brackertz¹¹). The results of systematic bacteriologic studies of the bacterial flora of the biliary tree and neighboring structures prove that the bile of the hepatic and common bile ducts is sterile in the absence of lithiasis, notwithstanding the proximity of the ducts to structures involved by focal infection. Primary suture of the common bile duct has no immediate inconveniences, and the late results of the procedure are excellent. Satisfactory results from the procedure have been obtained in 31 cases, which represent approximately three fourths of the cases of choledochal lithiasis in which an operation was performed during the last four years. In summarizing I find that nowadays things have been reversed: namely, primary suture of the common bile duct is the rule; Kehr's operation is the exception (fig. 4).

One of the primary reasons for abandoning primary suture of the common bile duct was that choleperitoneum developed. This complication was due to certain factors which prevented healing and induced early dehiscence of the wound, namely, the lack of objective knowledge of the anatomic and functional conditions of the common bile duct during the operation, the frequent trauma of the pancreas during examination with instruments, the use of violent maneuvers (especially in

11. Brackertz, W.: Tierexperimentelle Untersuchungen an den extrahepatischen Gallenwegen: I. Teil; Pankreasfermentschäden, *Deutsche Ztschr. f. Chir.* **237**: 141, 1932; II. Teil; Infektionschäden, *ibid.* **240**:707, 1933.

removing calculi lodged in the distal third of the common bile duct) and the incomplete removal of the concretions. However, the conditions are now quite different, since the surgeon has objective control of the biliary tree through cholangiography during operation, by means of which the remaining calculi and the degree of patency of the terminal segment of the common bile duct are visualized. He now completes his

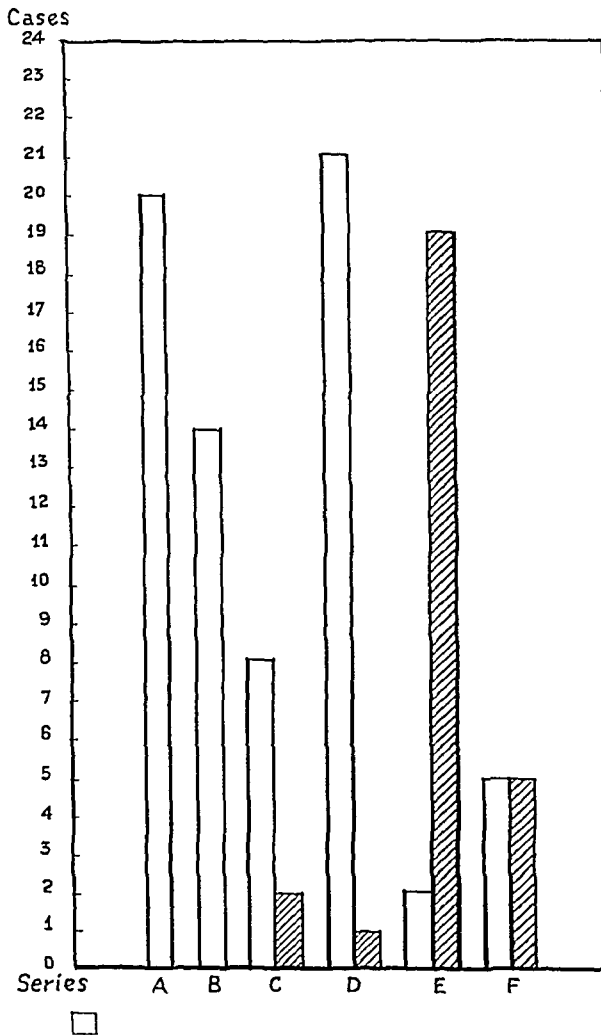


Fig. 4.—Graphic representation of the comparative frequency of Kehr's operation and of primary suture of the choledochus in several recent series of cases. The white columns signify Kehr's operation; the shaded columns represent primary suture of the choledochus.

work without interfering with the pancreas and resorts to primary suture of the common bile duct only when the synthesis of the continuity of the wound is perfect.

ADVANTAGES OF PRIMARY SUTURE

Primary suture of the common bile duct calls for thorough study of the system of the hepatic and common bile ducts, as well as for complete removal of the ductal concretions and determination of the degree of patency of the papilla of Vater.

As the elimination of bile through the intestine is reestablished, the excretory functions become normal, and the functional conditions of the liver improve. Avoiding external drainage means obviating certain disturbances which cause incomplete assimilation of food and deficient intestinal absorption of calcium (Cushny as quoted by Walters¹²), vitamins (Fromme¹³) and bile salts, with consequent development of general debility and insufficiency of organs of vital importance. Eliminating external drainage is the most effective measure for the prevention of postoperative cholerrhagia with its grave consequences, shown in the mortality rate of 64.7 per cent (Jesu¹⁴).

Whenever possible, placing of a tube in the duct, which is contractile and delicate, should be avoided. The indications for drainage should be diminished, and it is important that drainage should not be resorted to in patients exposed to infection and postoperative hemorrhage.

12. Walters, W.: *Obstructive Jaundice: Physiology and Surgical Aspects*, Rochester, Minn., Mayo Foundation, 1931, p. 27.

13. Fromme, A.: *Die Bedeutung der Vitamine für die Chirurgie*, Arch. f. klin. Chir. **189**:240, 1937.

14. Jesu, Y.: *La colerragia dopo drenaggio esterno delle vie biliari*, Arch. ital. di chir. **44**:101, 1936.

PROPHYLACTIC INTRAPERITONEAL INTRODUCTION OF CRYSTALLINE SULFANILAMIDE

EXPERIMENTAL OBSERVATIONS

HAROLD LAUFMAN, M.D.

AND

CATHERINE E. WILSON, M.S.

CHICAGO

The intraperitoneal use of crystalline sulfanilamide (powder) in the treatment of generalized peritonitis has aroused considerable interest in the past year. This is evidenced by the recent reports of Dees,¹ Thompson, Brabson and Walker² and Mueller,³ all enthusiastic over the possibilities of this form of treatment. After a thirty-six year survey of the mortality from peritonitis following appendicitis, Nassau, Lorry and Pulaski⁴ reported a sharp decrease in the mortality and attributed this to the use of sulfanilamide. Ravdin and his associates⁵ have found a lower mortality in peritonitis associated with appendicitis since the subcutaneous use of crystalline sulfanilamide in physiologic solution of sodium chloride was instituted.

In accord with the ever increasing use of the local application of sulfanilamide in the treatment of peritonitis and other infections, we thought it advisable to determine whether sulfanilamide is as valuable in preventing peritonitis as it is in curing the disease. Rosenberg and Wall⁶ recently carried out experiments in which they found that

This work has been aided by a grant from the Kuppenheimer Fund.

From the Division of Surgery of Northwestern University Medical School and the Departments of Surgery and Bacteriology of Michael Reese Hospital.

1. Dees, J. G.: Valuable Adjunct in Perforated Appendices (Intraperitoneal Use of Powdered Sulfanilamide), *Mississippi Doctor* **18**:215 (Sept.) 1940.

2. Thompson, J. E.; Brabson, J. A., and Walker, J. M.: The Intraabdominal Application of Sulfanilamide in Acute Appendicitis, *Surg., Gynec. & Obst.* **72**:722 (April) 1941.

3. Mueller, R. S.: Use of Powdered Crystalline Sulfanilamide in Surgery, *Correspondence, J. A. M. A.* **116**:329 (Jan. 25) 1941.

4. Nassau, C. F.; Lorry, R. W., and Pulaski, E. J.: Treatment of Appendicitis at Frankford Hospital: A Thirty-Six Year Survey of 4,650 Cases, *Arch. Surg.* **42**:296 (Feb.) 1941.

5. Ravdin, I. S.; Rhoads, J. E., and Lockwood, J. S.: Use of Sulfanilamide in Treatment of Peritonitis Associated with Appendicitis, *Ann. Surg.* **111**:53 (Jan.) 1940.

6. Rosenberg, S., and Wall, N. M.: The Treatment of Diffuse Peritonitis by the Direct Intraperitoneal Introduction of Sulfanilamide, *Surg., Gynec. & Obst.* **72**:568 (March) 1941.

sulfanilamide powder suspended in physiologic solution of sodium chloride and injected into the peritoneal cavities of rats was of definite curative value when introduced simultaneously with a mixture of bacteria. This treatment was somewhat less valuable when the peritonitis had already been present for four to eleven hours. They suggested that the intraperitoneal route has advantages over the parenteral route but that in the human being the initial instillation must be supplemented by subsequent subcutaneous injections in order to maintain a satisfactory blood level.

In our experiments we used 108 rats and performed laparotomies on 54; we introduced the powder directly into the peritoneal cavity. This was done in order to simulate more closely the procedure carried out in the human subject. The remaining animals were used as controls.

BACTERIA USED TO PRODUCE PERITONITIS

We used a mixture of cultures of *Bacterium coli* and *Streptococcus faecalis*. The strain of *B. coli* was isolated from the exudate in a case of human peritonitis and was carried through three mouse passages (our preliminary experiments were carried out on mice). As the experiments with rats continued, *B. coli* was cultured from the dead controls and used. The strain of *Str. faecalis* was isolated from the stool of a human being and washed in physiologic solution of sodium chloride. This was never recultured from the dead controls, so the original strain was used throughout. Our mixture of cultures contained equal quantities of the two strains of bacteria, approximately 2,500,000,000 of each per cubic centimeter. To 10 cc. of the mixture 2 cc. of mucin was added.

METHOD

Eight rats were used to standardize the dose of the culture mixture which when injected intraperitoneally would cause the death of the animal in twenty-four hours from peritonitis. It was found that 0.5 cc. of the culture mixture would usually accomplish this end. We used on the average 300 mg. of sulfanilamide powder for each of our rats, which weighed from 150 to 250 Gm.

The first experiment consisted of introducing the culture and the sulfanilamide powder simultaneously at the time of laparotomy. In the second experiment, sulfanilamide was inserted alone, the abdomen closed and the bacteria injected intraperitoneally by needle four hours later. This would give us an evaluation of the intraperitoneal use of sulfanilamide powder as a prophylactic agent. The third experiment consisted of the simultaneous introduction of the culture and the drug and, in addition, repeated subcutaneous injections of an 0.8 per cent solution of sulfanilamide in physiologic solution of sodium chloride. The fourth experiment consisted of injecting the culture intraperitoneally by needle and performing a laparotomy for the introduction of sulfanilamide one and one-half hours later in some animals and five hours later in others. Ether anesthesia was used throughout. The abdomens were treated with alcohol before incision. A through and through silk suture was used for closure.

RESULTS

Experiment 1 (0.5 cc of culture mixture and 300 mg. of sulfanilamide powder introduced simultaneously by laparotomy).—This procedure was carried out on 15 rats. A control series of 15 rats received an intraperitoneal injection of the same amount of the culture mixture used in the laparotomized rats, but received no sulfanilamide. Eleven of the laparotomized rats were alive and well when put to death

TABLE 1.—Summary of Experimental Results

Rats Used		Rats Surviving 24 Hours	Rats Surviving 2 Weeks
Experiment 1.	Simultaneous introduction of culture mixture and sulfanilamide at laparotomy		
	15 treated animals	11 (73+%)	9 (60%)
	15 controls	3 (20%)	2 (13%)
Experiment 2.	Prophylactic introduction of sulfanilamide four hours before injection of culture mixture		
	15 treated animals.	15 (100%)	11 (73+%)
	15 controls	2	2 (13.3%)
Experiment 3.	Simultaneous introduction of culture mixture and sulfanilamide followed by subcutaneous injections of sulfanilamide solution		
	12 treated animals.	10 (83+%)	7 (58%)
	10 controls	0	0
Experiment 4	Introduction of sulfanilamide after peritonitis had become established		
	6 animals treated 5 hr after infection	2 (33+%)	1 (17%)
	6 animals treated 1½ hr after infection	1 (17%)	1 (17%)
	6 controls	0	0

TABLE 2.—Comparison of Survival Periods of Treated Animals

Experiment	Percentage of Rats Alive at 24 Hours	Percentage Alive at 2 Weeks
1 Simultaneous introduction of sulfanilamide and culture mixture	73+%	60%
2 Prophylactic introduction of sulfanilamide	100%	73%
3 Simultaneous introduction of sulfanilamide and culture mixture followed by subcutaneous injection of sulfanilamide solution	83+%	58%
4 Active treatment of peritonitis with sulfanilamide		
5 hours after infection	33%	17%}
1½ hours after infection.	17%	17%} 34%

two weeks after the experiment. Despite their appearance of well-being, each of these animals nevertheless had peritonitis in some degree when killed. Four of the treated animals died in twenty-four hours, 3 within forty-eight hours and 2 within seventy-two hours. Twelve of 15 controls were dead within twenty-four hours and 1 within forty-eight hours; 2 lived on apparently well.

Experiment 2 (300 mg. of sulfanilamide powder introduced intraperitoneally by laparotomy; 0.6 cc of culture mixture injected four hours later).—This experiment was carried out on 15 rats. A control

series of 15 rats received only the injection of culture mixture. Ten of the rats operated on remained alive and were apparently well fourteen days after the experimental treatment; 2 lived forty-eight hours, and 2 lived seventy-two hours. All but 2 of the control animals were dead in less than twenty-four hours; these 2 remained alive and apparently well.

Postmortem examination revealed a seropurulent peritonitis in most of the rats. Postmortem cultures of material from all the rats yielded only *B. coli*.

Experiment 3 (0.6 cc. of culture mixture and 300 mg. of sulfanilamide powder introduced simultaneously; subsequent subcutaneous injections of 0.8 per cent solution of sulfanilamide in physiologic solution of sodium chloride).—This experiment was begun on 12 rats. Five cubic centimeters (40 mg.) of the sulfanilamide solution was injected subcutaneously (2.5 cc. in each flank) three times a day for two days after operation. Seven of these rats were alive and apparently well two weeks after operation; 2 lived only twenty-four hours; 2 lived forty-eight hours, and 1 lived seventy-two hours. All of the controls were dead within twenty-four hours, half of them dying within twelve hours.

Postmortem examination revealed serosanguinous or seropurulent peritonitis. Cultures yielded only *B. coli*.

Experiment 4 (injection of 0.5 cc. of culture mixture; laparotomy later with introduction of 300 mg. of sulfanilamide powder).—When the abdomens of the animals were opened as early as one and one-half hours after the injection of the culture mixture, there was already seropurulent generalized peritonitis. The drug was introduced in 6 rats one and one-half hours after the injection of the culture mixture and in 6 others five hours after the injection. Four in the former group and 5 in the latter group died within twenty-four hours. Only 1 in each group remained apparently well two weeks after operation. All of the control animals in this experiment were dead within twenty-four hours.

Postmortem examination revealed seropurulent peritonitis, and the cultures yielded only *B. coli*.

COMMENT

Sections taken from the peritoneums of rats which received only sulfanilamide powder revealed a moderate degree of edema and a mild exudative and fibroplastic reaction. Similar sections taken from rats in which starch was introduced intraperitoneally revealed a much more severe type of polymorphonuclear response. We mention this to show that sulfanilamide powder is relatively nonirritating as a foreign body when placed in the peritoneal cavity.

It is well known that the drug is readily absorbed from the peritoneum into the blood stream, so that besides its local action there is no doubt a systemic action, which in turn has its own effect on any intraperitoneal infection.

The results of experiment 2, in which sulfanilamide was placed in the peritoneal cavity four hours before the injection, indicate that the prophylactic local use of the drug has merit. A greater percentage of these animals survived than of those in any of the other experiments.

Our poorest results were obtained in experiment 4, in which the drug was introduced after the peritonitis was already existent. Our cultures were apparently more lethal than those used by Rosenberg and Wall, since most of our unprotected animals died within twenty-four hours. We were unsuccessful in saving the lives of 9 of 12 rats which had an already established peritonitis of only one and one-half to five hours' duration, while Rosenberg and Wall were able to bring about recovery in some rats in which peritonitis had been present for twenty hours. This discrepancy emphasizes the factor of variation in the virulence of the infection in cases of peritonitis from different causes, a factor making it difficult to determine accurately the value of intraperitoneal chemotherapy. The only criteria for accurate comparison are the control experiments.

As important as the virulence of the organisms is the time allowed for the infection to develop. When sulfanilamide was introduced intraperitoneally at the same time as the infection, 9 of 15 rats lived two weeks, while only 2 of 15 controls survived. When subsequent subcutaneous injections of sulfanilamide were administered, a slightly better recovery rate was observed. As stated, our results with sulfanilamide after peritonitis had become established were poor.

On the other hand, all of the rats which received a prophylactic intraperitoneal dose of sulfanilamide were alive after twenty-four hours, while all but 2 of the controls were dead. We felt that this finding was impressive enough to allow these animals to go without subsequent subcutaneous injections of the drug. As a result, 11 of 15 survived and were apparently well after two weeks.

SUMMARY

It has been known for some time that the prophylactic use of sulfanilamide and its derivatives is of great value in the prevention of severe infections in surface wounds.⁷ Our experiments indicate that this principle also applies to inflammation of the peritoneum, and that the intraperitoneal use of sulfanilamide powder need not be limited to

7. Chemotherapy of War Wounds, Foreign Letters (London), J. A. M. A. 14:1683 (April 27) 1940.

cases of active peritonitis. Our best results were obtained when sulfanilamide powder was introduced four hours before the culture mixture was injected. Our poorest results were obtained when the drug was administered after peritonitis had become established. Although our results cannot be considered conclusive, we offer the suggestion that in those cases in which there is any question of peritoneal contamination occurring during an operative procedure, it might be wise to introduce a prophylactic amount of sulfanilamide powder into the peritoneal cavity. It is comparatively nonirritating to the peritoneal surface.

The sulfanilamide powder was supplied by Eli Lilly and Company, Indianapolis.

Mr. Louis S. Cholden gave technical assistance and Dr. Katharine M. Howell guidance and advice in the preparation of this paper.

LARGE RETROPERITONEAL CHYLOUS CYST

REPORT OF A CASE, WITH EXPERIMENTS ON LYMPHATIC PERMEABILITY

FERDINAND C. LEE, M.D.

BALTIMORE

The purposes of this article are, first, to report a case of large retroperitoneal chylous cyst and, second, to advance a new explanation for the formation of a cyst of this sort on the basis of experimental work on lymphatics.

REPORT OF CASE

G. C., a white man 47 years old and a tailor by occupation, came to the Johns Hopkins Hospital with the complaint of rupture.

Previous History.—His general health had been good. There had been no abdominal symptoms except occasional postprandial eructations and moderate constipation which required the use of cathartics twice a week. There had been no jaundice or melena. When 19 years old, he had had gonorrheal infection.

Present Illness.—About seventeen years before admission, he noticed a small swelling about the size of the end of his thumb in the midline of the epigastrium. The mass gradually increased in size without producing any symptoms until five months before admission, when he had abdominal pain that persisted for four days. The pain was moderately severe, not cramplike, but constant and generalized; there was no vomiting or increase of constipation, but there was possibly some distention. He remained home for four days and then was free of any trouble until a week before admission, when he had three successive attacks of pain, about a day apart, in the upper part of his abdomen. The pain was severe and radiated to the back and to both shoulders and was present during the day. His abdomen was again apparently distended; he eructed a great deal, and it required two enemas to relieve the constipation. Vomiting occurred in only one of the attacks. He had lost about 5 pounds (2.3 Kg.) during the past year.

Physical Examination.—The patient was a well nourished and well developed Italian, 5 feet 2 inches (157.5 cm.) tall. The abdomen was protuberant, and about 6 cm. above the umbilicus there was a hernial protrusion through a ring that measured about 4 cm. in diameter. The mass was slightly tender and could not be reduced completely. It was obviously an epigastric hernia and as such could have accounted for all the symptoms. Other than this the examination yielded negative results. The blood pressure was 125 systolic and 80 diastolic.

Laboratory Data.—The white blood cell count was 9,000. The hemoglobin content was 88 per cent. The Wassermann test was negative. Examination of the urine gave negative results. Roentgen examination of the chest showed the lungs to be clear.

From the Department of Surgery, Johns Hopkins University.

Operation.—On May 3, 1932, with the patient under anesthesia induced with avertin with amylene hydrate and ether, the hernial sac was opened and found to contain besides the peritoneal fat a small amount of thin milky fluid. A culture was taken which later proved to be sterile. Palpation through the hernial ring was not satisfactory, and no pathologic growth was felt. The hernia was repaired with silk suture, and the wound healed without any complications. On May 14, the patient was examined by a medical consultant, but no pathologic process was discovered. The differential blood count was as follows: polymorphonuclear neutrophils, 81 per cent; polymorphonuclear basophils, 1 per cent; polymorphonuclear eosinophils, none; lymphocytes, 16 per cent; monocytes, 2 per cent. On May 16, a roentgen report of a flat plate of the abdomen revealed no abnormalities. A fluoroscopic examination on the following day showed no mediastinal masses; the aorta was moderately dilated; the diaphragmatic excursions were normal.

Subsequent Course.—The patient remained in good health until May 1, 1935, when he was readmitted because of distention and abdominal pain. Apparently for three months before admission he had noticed a gradual and progressive enlargement of the abdomen. At first there was no pain, nausea or vomiting. However, his appetite failed, and he felt bad generally. He had lost about 10 pounds (4.5 Kg.). No fever was noticed.

About two and a half weeks before admission he noticed a sharp constant pain in the lower part of the abdomen on the right side. There was also a mass in this region. The pain gradually increased in severity, particularly when he was in a sitting position. He obtained greatest relief by lying on his back and flexing his thighs. The mass increased in size so that it spread across the entire lower part of the abdomen, but in spite of this he was not greatly inconvenienced, since he followed his occupation until the day of admission to the hospital. There was no nausea, vomiting, constipation, diarrhea, melena or jaundice.

Physical Examination.—His temperature was 99.4 F. His pulse rate was 116 and his respiratory rate 20. The examination again yielded essentially negative results except for considerable enlargement of the abdomen. The scar from the previous operation for epigastric hernia was well healed. The abdomen was distended by a large mass which had three large lobules; one lobule was in the center, and the other two were in the right flank. The whole mass was smooth and not tender. It was possible to dislocate it a little in all directions. There was no local heat or fluctuation. The percussion note over the mass was dull. Superficial veins in the abdominal wall were not enlarged, but the veins in the legs were prominent; there was also slight pitting edema at the ankles. The blood pressure was 145 systolic and 90 diastolic.

Laboratory Data.—The white blood cell count was 6,720. The hemoglobin was 97 per cent. The differential blood cell count was normal. Roentgen studies showed a normal colon with a mass which was entirely extraintestinal. The stomach and duodenum were normal. A large cystic tumor occupied the right side of the abdomen and extended as far as the symphysis pubis.

Diagnosis.—In view of the small amount of chylous fluid observed at the previous operation, it was felt that the large mass was probably another example of chylous cyst obstruction; for that reason a diagnosis of chylous cyst was made. Echinococcic cyst was also considered a possibility.

Operation.—On May 2, with the patient under anesthesia induced by avertin with amylene hydrate supplemented with nitrous oxide and ether anesthesia, a small incision was made in the lower part of the right rectus muscle. A small amount



Fig. 1.—Roentgenogram made after patient had been given a barium sulfate meal to show how the large chylous cyst had pushed most of the small intestine into the lower left quadrant of the abdomen.



Fig. 2.—A lateral plain roentgenogram of the abdomen showed the outline of the cyst; the artist used the film to trace on the same scale the location of the cyst with reference to the bony landmarks. From observations made at the time of operation it was possible to put in the broad base and the bosses of the cyst.

of clear amber fluid escaped when the peritoneum was opened. The mass proved to be reddish gray with a smooth and glistening surface. Palpation revealed that the fluctuant mass had a large broad base the center of which was near the bifurcation of the aorta. Removal of the tumor was out of the question. All of the small intestine was pushed to the left side of the abdominal cavity, as the roentgenograms had indicated (fig. 1). After packing off the peritoneal cavity, a needle was inserted into the mass, and a thick white creamy homogeneous substance was aspirated. After the needle had been withdrawn, the white material continued to pour out through the needle hole; this indicated that the pressure in back of it was high. The needle hole was enlarged at once, and the nozzle of the aspirator was inserted into the middle of the cyst; however, the material was too thick for the small holes in the cylindric aspirator, necessitating the introduction of a simple open end tube. The cyst was then rapidly evacuated; 3,940 cc. was obtained. With the decrease in the volume of the cyst it was possible to bring its collapsed walls out of the incision and to marsupialize it with catgut sutures. A piece of the cyst wall was taken for microscopic examination. Some bleeding occurred from the inner surface of the cyst, and it was necessary to control this hemorrhage with five catgut transfixion sutures. The inside of the cyst was moderately smooth, having three depressions corresponding to the lobules. A large rubber catheter was passed to the bottom of the cyst and sutured to the mouth of the opening. In addition a Penrose drain with its gauze removed was also placed into the cavity. A petrolatum gauze pack was placed around the opening of the cyst, interrupted catgut sutures were put in the anterior rectus sheath, and the skin around the drains was approximated with interrupted silk sutures. Figure 2, drawn from a lateral preoperative roentgenogram, gives a good idea of the cyst.

The patient made an uneventful recovery, draining 50, 150, 175, 100 and 60 cc. respectively in the first five days after operation. The material was the same as that found in the cyst, only slightly thinner, and at first blood stained. At no time did his temperature exceed 99.4 F. The drains were replaced on the seventh post-operative day with a small protective wick which was allowed to remain for seventeen days.

The patient was discharged from the hospital on May 27 with a small amount of drainage which became gradually less, the wound being completely healed on June 13.

Postoperative Laboratory Reports.—Examination of the fluid from the cyst immediately after operation showed the contents to be pure fat with no cells, organisms or signs of echinococcic infection.

Examination of the histologic section of the cyst wall found it to be of varying thickness and composed essentially of dense granulation tissue, with the older fibrous tissue situated at the periphery (fig. 3). There was much round cell infiltration and an abundance of eosinophils and plasma cells. Numerous relatively large blood vessels were seen, chiefly near the lumen. A thin, fibrinous deposit covered the peritoneal surface of the cyst. The lumen had no membrane but instead showed a thick layer of fat-laden monocytes which were partly surrounded by a thin network of fibroblasts that extended a slight distance into the lumen (fig. 4). A special stain failed to show any elastic tissue in the cyst wall. The Bodian nerve stain, which was so satisfactory in other tissue work, failed to show any nerve fibers.

Diagnosis.—The diagnosis was chronic inflammatory retroperitoneal chylous cyst.

At the time of writing, the patient has been back at work six years since operation without any sign of recurrence of the cyst. Because of an attack of

slight discomfort in the upper part of the abdomen after meals, a roentgenogram of the gallbladder was taken on Jan. 27, 1940; no lesion was seen.

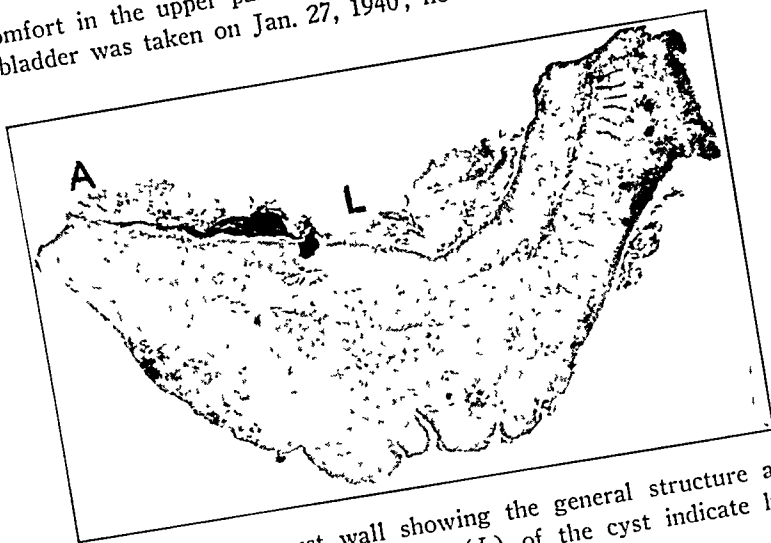


Fig. 3.—Section of the cyst wall showing the general structure and varying thickness; the dark masses in the lumen (L) of the cyst indicate hemorrhage; an enlargement of the area A is shown in figure 4.

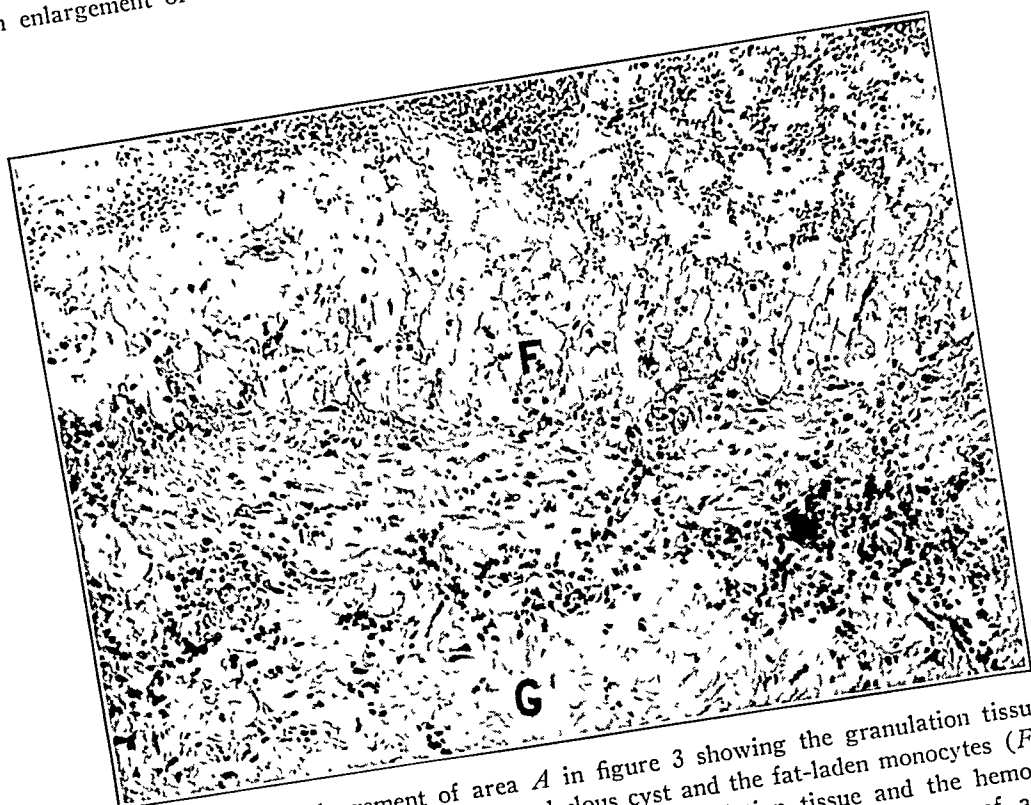


Fig. 4.—An enlargement of area A in figure 3 showing the granulation tissue (G) which composed the wall of the chylous cyst and the fat-laden monocytes (F) which formed the transition zone between the granulation tissue and the hemorrhagic exudate within the lumen of the cyst. There was no evidence of any lining membrane for the cyst.

COMMENT

The account of the present illness has been given in detail because the symptoms may have been due to a lesion of the abdominal lymphatic system instead of to epigastric hernia. The literature on retroperitoneal chylous cysts, with especial reference to the lymphangiomas, was summarized in 1939 by Gerster¹ in connection with a report of a case of his own. Although retroperitoneal chylous cysts are rare (only about 20 having been reported), new ones are constantly being recorded.² The cyst just described, containing 3,940 cc. of chyle, was one of the larger ones. It is exceeded in size only by those described by Sarwey³ (6,200 cc.), Hadley⁴ (1½ gallons [5,678 cc.]), Bonnet⁵ (6,000 cc.) and Narath⁶ (4,000 cc.). The unusual case of Koblanck and Pforte⁷ (25 liters) was one of hydronephrosis and not of chylous cyst.

A classification of these retroperitoneal and mesenteric cysts has been made along etiologic lines by Warfield,⁸ who listed the following sources: (1) embryonic retroperitoneal organs; (2) displaced embryonal intestinal tissue; (3) dermal inclusions; (4) angiomas of blood and lymph vessels; (5) necrosis of lymph nodes (e.g., that in tuberculosis) or of solid tumors (e.g., lipoma); (6) trauma or foreign bodies; (7) lymphatic obstruction.

In the last-named category it is proposed to put the case reported, except that it is felt that a possibly new explanation may be advanced for the formation of the cyst. It is believed that the cyst may have developed as follows: A small extravasation occurred in one of the small lymph glands near the root of the mesentery. As the chyle escaped into the retroperitoneal space, there was a reaction of the tissues so that the extravasation began to be walled off. Since, however, the rent in the wall of the lymph vessel was not closed over by a clot of

1. Gerster, J. C. A.: Retroperitoneal Chyle Cysts with Especial Reference to the Lymphangiomata, *Ann. Surg.* **110**:389-409, 1939.

2. Brady, L.: A Further Study of Extraperitoneal Pelvic Conditions in Women, *Am. J. Obst. & Gynec.* **32**:577, 1936.

3. Sarwey, O.: Ein Fall von retroperitonealer Chyluscyste bei einem 11 jährigen Mädchen: Extirpation; Heilung, *Centralbl. f. Gynäk.* **221**:407, 1898.

4. Hadley, M. N.: The Origin of Retroperitoneal Cystic Tumors, *Surg., Gynec. & Obst.* **22**:174, 1916.

5. Bonnet, cited by Speckert, J.: Ein Fall von Chyluscyste, *Arch. f. klin. Chir.* **75**:998, 1905.

6. Narath, A.: Ueber retroperitoneale Lymphcysten, *Arch. f. klin. Chir.* **50**:763, 1895.

7. Koblanck and Pforte: Hydronephrose mit chylusähnlichen Inhalt und eigenartiger Wand, nebst Bemerkungen über Chylus-Cysten, *Virchows Arch. f. path. Anat.* **161**:44, 1900.

8. Warfield, J. O.: A Study of Mesenteric Cysts with Report of Two Cases, *Ann. Surg.* **96**:329, 1932.

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lymph and chyle therefore continued to flow into an area which was getting larger and which was being circumscribed more and more effectively, lymphatic mesothelium at the point of rupture was not able to seal off the defect but lined the mouth of the extravasated area and extended partly along the fibrous tissue neck of the bulbous mass without ever lining the cyst completely (fig. 4). On this basis it is understandable why a chylous cyst with a thin wall should have a mesothelial lining; such a cyst always did have a complete specialized lining and did not need granulation tissue to form an artificial wall.

The extent to which the cyst is lined by mesothelium may determine the length of time during which drainage of the marsupialized pouch may continue. If the lymphatic mesothelial cells are only at the neck of the sac, a clot will soon form and close the stoma. However, if the lining of the cyst is extensive, then chyle will continue to collect for a relatively long while, and it may be months before drainage will finally cease.

It is difficult to see how the presence of chylous fluid in these cysts can be explained on any other basis than a direct connection with chyle-bearing lymph vessels. Repeated collection of the chylous fluid after one or more aspirations would indicate such a connection.⁹ The position of chylous cysts, occasionally relatively far from normal chyle channels, can be explained by an abnormal course of the lymph flow due to developmental defects or to obstruction subsequent to inflammation or tumors. That such unusual pathways for chyle occur is attested by the cases of chylous fistula, as, for instance, of the thigh,¹⁰ of the abdomen¹¹ and of the scrotum.¹² It seems less likely that chyle would effuse into a preformed cystic cavity¹³ or that degeneration of the wall of the cyst¹⁴ would give rise to its extensive white fatty contents.

However, it is also difficult to explain how a rupture of a lymph vessel may occur unless one falls back on a local weakness of the vessel wall due either to a developmental defect or to a pathologic process. That the rupture may occur in the lymph gland is possible because

9. Volkmann, J.: Ueber Chyluscysten am Halse, Beitr. z. klin. Chir. **146**:654, 1929. Sarwey.³ Hadley.⁴

10. Munk, I., and Rosenstein, A.: Zur Lehre von der Resorption im Darm nach Untersuchungen an einer Lymph (Chylus-) Fistel beim Menschen, Virchows Arch. f. path. Anat. **123**:230, 1891.

11. Fetzner, W.: Ein Fall von eigenthümlicher Erkrankung der Lymphgefäße, Arch. f. physiol. Heilk. **8**:128-132, 1849.

12. Carter, H. V.: On the Connection Between a Local Affection of the Lymphatic System and Chylous Urine, Med.-Chir. Tr. London **45**:189-207, 1862.

13. Dowd, C. N.: Mesenteric Cysts, Ann. Surg. **32**:515, 1900.

14. Henschen, K.: Beiträge zur Geschwulstpathologie des Chylusgefäß-systems, Inaug. Dissert., Zurich, 1905.

lymph nodes have been found in the walls of mesenteric cysts.¹⁸ Experimentally, as hereinafter mentioned, such ruptures were seen to occur. Since a clinical chylous fistula of the thigh necessitates the formation of unusual lymphatic pathways and pressure relations in addition to probable congenital abnormalities or acquired pathologic processes which finally terminate in complete penetration of the relatively thick skin, it is no more difficult to believe that a relatively thin lymph vessel in the abdomen may rupture and give rise to a chylous cyst.

Symptoms.—There is as yet no symptom or group of symptoms which is pathognomonic for a retroperitoneal chylous cyst. The cysts, when small, are symptomless and are found incidentally at operation or necropsy. Only when the cysts become larger and exert pressure on contiguous structures do symptoms appear. Enlargement of the abdomen may be the first sign, followed by a loss of appetite. Pain, at first dull but constant, precedes nausea; vomiting is rare. Alternating attacks of diarrhea and constipation have been reported. Urinary frequency may appear early, but it rarely brings the patient to the physician. A slight loss of weight is common in spite of the increase in the size of the abdomen.

Diagnosis.—The diagnosis has usually been made by needle puncture. However, this method is not recommended, not only because chyle may thus escape into the peritoneal cavity but because the bowel may be punctured. The only reason the diagnosis was made in the case reported was because of the slight chylous ascites observed when the epigastric hernia was repaired. Valuable help was given by lateral roentgenograms of the abdomen, since they and not the anteroposterior views showed the smooth round character of the mass.

Briefly, some of the anomalies from which retroperitoneal chylous cyst must be distinguished and some aids to the differential diagnosis are: ovarian cyst—slow development, pelvic adhesions, menstrual disturbance, progressive weakness, dyspnea, swollen feet; pancreatic cyst—early pain in the upper part of the abdomen, not uncommonly previous cholecystitis or pancreatitis, epigastric mass (usually in the midline), abnormal appearances in roentgenograms of the intestinal tract; echinococcic cyst—slow growth, usually associated with the liver, presence of a pedicle in some instances, venous obstruction, complement fixation test; omental cyst—rarely large size, slow growth, occasional colicky pains, superficial location, movability; pedunculated myoma of the uterus—menorrhagia, bladder irritability, pain worse at menstrual periods, movable growth, usually rounded projection; hydrops of the gallbladder—location on the right side, superficial involvement, continuous with liver dulness; retroperitoneal tumor—commonly sarcoma, nodular type, deep location, loss of weight, ascites, metastases; enlargement of the

spleen—gradual protrusion from under the left costal margin, early pain from adhesions, blood abnormalities; neoplasm of the bowel—relatively small size, paroxysmal pain, blood in the stool, loss of weight, pathologic roentgen findings; movable kidney—pain radiating to the bladder, radial displacement, pathologic urinary findings, pyelographic evidence; hydronephrosis—intermittent pain, disappearing tumor, pyelographic evidence; tuberculous abscess—tuberculous infection elsewhere, slow onset, location in upper part of the abdomen, fever, weakness, loss of weight, possibly spinal caries; pregnancy.

Of the complications that have occurred with chylous cysts, the most serious has been intestinal obstruction due to volvulus, adhesions or simple mechanical compression. The mortality in such cases, usually involving resection of a part of the intestine, has been given as 50 per cent. Rupture of the cyst is rare and usually due to trauma. A malignant change in the cyst wall has been mentioned.¹⁵

Treatment.—The best treatment is excision if it is possible. Marsupialization has been successful in those instances in which operative removal was not possible, and even with this conservative method the mortality has been put at 16 per cent.¹⁶ Aspiration, obviously, has no curative value.¹⁷

EXPERIMENTS

If the chylous cysts are formed because of lymphatic obstruction, experimental obstruction might give rise to the formation of such cysts. However, in cats and dogs cysts were never formed either after ligation of the thoracic duct in the chest¹⁸ or subsequent to much more elaborate measures taken to obstruct the flow of lymph.¹⁹ The measures included not only ligation of the thoracic duct in the chest but also ligation of both lymph ducts in the neck, subtotal removal of the cisterna chyli, ligation of the superior vena cava and multiple injections of sodium morrhuate in and about the lymph trunks.

Since obstruction did not produce cysts, it seemed possible that the production of a great many openings and sections of lymph trunks in

15. Hertzler, A. E.: *Disease of Peritoneum*, in Graham, E. A.: *Surgical Diagnosis by American Authors*, Philadelphia, W. B. Saunders Company, 1930, vol. 2, p. 589.

16. Roller, C. S.: *Mesenteric Cysts: A Brief Discussion and Report of Three Cases*, *Surg., Gynec. & Obst.* **60**:1128, 1935.

17. Slocum, M. A.: *Surgical Treatment of Chylous Mesenteric Cysts by Marsupialization*, *Am. J. Obst. & Gynec.* **41**:464, 1938.

18. Lee, F. C.: *The Establishment of Collateral Circulation Following Ligation of the Thoracic Duct*, *Bull. Johns Hopkins Hosp.* **33**:21, 1922.

19. Blalock, A.; Robinson, C. S.; Cunningham, R. S., and Gray, M. E.: *Experimental Studies on Lymphatic Blockage*, *Arch. Surg.* **34**:1049 (June) 1937.

order that the young regenerating lymphatic endothelium would not be strong enough in closing over the defects to resist the endolymphatic pressure might give rise to a cystic formation.

To that end the thoracic duct in each of 5 cats was ligated in the chest; in addition the intestinal lymph trunks together with the mesenteric lymph gland and all the other smaller lymph glands situated nearer the intestine were removed from the duodenum to the colon. Except for the presence of chylous ascites which persisted for the first three days, the animals showed no ill effects; and when they were killed from two weeks to two months after operation, no cysts were seen. The collateral lymph circulation which had developed was mainly an enlargement of the fine lymph plexus which accompanied the mesenteric vessels. Apparently all the openings in the lymph system caused by the operative intervention were sealed off by thrombosis.

Another method was tried. In 1932, Drinker and Field²⁰ reported that when the pressure was raised on a graphite suspension which was being injected into a lymph vessel of the frog's tongue, extravasations were seen to occur, indicating a rupture of the vessel wall.

To repeat, in a measure, this type of experiment, the thoracic duct was ligated in 11 cats and 1 dog and then either one hour to twenty-four hours later, with the animals under intratracheal ether anesthesia, the mesenteric lymph vessels were injected either with india ink or with a 3 per cent aqueous solution of trypan blue. In addition, in 4 animals under ether anesthesia whose thoracic ducts had not been ligated, the lymph trunk was clamped at the mesenteric gland after the injection of india ink had been started; thus an obstruction was produced between the gland and the site of injection. In only 3 instances did a definite rupture of the lymph vessel with extravasation occur.

The first example occurred in a cat whose thoracic duct had been ligated in the chest twenty-four hours before. As the trypan blue solution was being injected through a no. 27 gage needle attached to a 10 cc. syringe, a small by-pass to the main channel filled and suddenly ruptured, causing the trypan blue to extravasate between the leaves of the mesentery. It was not possible to determine the pressure that was exerted on the injected fluid within the vessel, but at best the pressure of a stream of fluid from the end of a no. 27 gage needle must of necessity be relatively small.

The second rupture was noticed under similar conditions except that commercial india ink was used. In this case a subsurface lymph vessel in the mesenteric lymph gland ruptured and gave rise to a large extravasation.

The lymph gland was also the site for the third rupture. In this instance a dog was used whose thoracic duct had been ligated in the chest one hour before. The injected mass was commercial india ink which had been dialyzed against solution of sodium chloride.

Finally, it was noticed that while trypan blue or india ink was being injected into the mesenteric lymphatics with the thoracic duct ligated occasionally the junction point where a vessel divided or was joined by a collateral vessel would become larger, like a small bay, and that some of the ink particles would work

20. Drinker, C. K., and Field, M.: The Lymph Capillaries in the Web of the Frog, *Am. J. Physiol.* **100**:642-649, 1932.

their way through the vessel wall and lodge in the perivascular tissue without causing a definite rupture. The phenomenon of permeation of the lymph vessel wall without rupture by a relatively large particle like india ink was commonly seen in the mesenteric lymphatics when the pressure on the injected fluid was raised and maintained for a few minutes, the thoracic duct having been previously ligated.

SUMMARY

A case in which a large retroperitoneal chylous cyst was correctly diagnosed and the patient successfully treated by marsupialization is reported. A new explanation for the formation of a thick-walled chylous cyst is advanced, namely, that the cyst forms when a chyle-bearing lymph vessel is ruptured and the extravasation of the chyle is limited by the formation of a wall of granulation tissue.

In experiments on animals, a high degree of obstruction to the lymph flow was produced, but there was no production of cysts. However, in 3 animals rupture of a small lymph vessel was directly observed while material was being injected into the lymph channel. This supports the view that the wall of a lymph vessel may rupture and that a chylous cyst may develop from the extravasation. The relative ease with which carbon particles may traverse the wall of a lymph vessel without causing rupture was also observed.

TOTAL GASTRECTOMY

INDICATIONS FOR OPERATION WITH A REPORT OF FOUR CASES

CHARLES BRUCE MORTON II, M.D.

Professor of Clinical Surgery and Gynecology

UNIVERSITY, VA.

Total gastrectomy is no longer a surgical curiosity, but because of its technical difficulties it may never become commonplace. Relatively few patients are encountered in whom the indications for the operation accepted at present are fulfilled. These indications are: first, disease of the stomach endangering life; second, such extensive involvement of the stomach that nothing short of total gastrectomy will serve to eradicate the disease, and third, confinement of the disease to the stomach alone. The practicability of the operation is determined by the mobility of the stomach and the esophagus and by the general condition of the patient. A malignant neoplasm of the stomach is ordinarily the only disease which necessitates total gastrectomy.

The anatomy of the stomach is such that the organ offers a ready path for the spread of malignant cells from each part to every other part. The muscular distribution, the vascular channels, the lymphatic pathways and the tissue spaces all contribute their part to the permeation of carcinoma through the stomach. The pathologist in performing necropsy on patients who have succumbed to operation and in examining specimens removed by the most radical subtotal gastrectomy frequently has the experience of demonstrating malignant cells in the stomach far beyond the grossly evident borders of a given tumor. In other words, no matter how wide a margin the surgeon may believe he is providing in performing radical subtotal gastrectomy he still may leave microscopically demonstrable tumor which will eventually cause local recurrence and possibly metastasis of the original tumor.

Although Livingston and Pack¹ in their monumental statistical study of the end results of the treatment of gastric cancer demonstrated remarkably good results of subtotal gastrectomy in the hands of the most capable surgeons, there is still much room for improvement, even in the treatment of readily resectable carcinoma. Livingston and Pack showed that patients with carcinoma of the stomach when operated on by the average or occasional surgeon fare badly. Not only the operative

From the Department of Surgery and Gynecology of the University of Virginia.

1. Livingston, E. M., and Pack, G. T.: *End Results in the Treatment of Gastric Cancer*, New York, Paul B. Hoeber, Inc., 1939.

mortality rate but also the end results of the average surgeon have shown little or no improvement since the early days of gastric surgery around 1880.

Disregarding for the moment the cause of the high operative mortality, it is probable that in terms of end results the difference between the subtotal gastric resection of the expert gastric surgeon and that of the surgeon who performs gastrectomy only infrequently is largely one of the amount of tissue removed. Gastrojejunostomy may be much more difficult when only a little of the stomach remains, especially if exposure is difficult because of poor anesthesia, inexperienced assistance or other factors that may plague the occasional operator. Widespread removal of adjacent lymph glands and lymphatics also is essential for good prognosis. The expert accomplishes it as a matter of course; the inexperienced surgeon for various reasons frequently neglects it.

In all patients surviving the operation itself, excluding those who die soon of natural causes or intercurrent trouble, the failure to obtain a long time cure results either from recurrence of the tumor locally or regionally or from metastasis to some distant site. Certainly local recurrence in the remaining part of stomach or the reappearance of tumor in the regional lymph glands and lymphatics or in other adjacent structures is much more frequent than distant metastasis. Ewing² stated: "Recurrences [after operation] are chiefly in liver, peritoneum, and retroperitoneal nodes." In 20 consecutive instances of known recurrence in my own cases this statement was borne out. In addition, however, 4 patients were shown to have recurrent cancer in the stump of the stomach although radical subtotal gastrectomy had been performed. Therefore, the more radical the operation in terms of removal of the stomach itself and of the adjacent lymph glands and lymphatics, the greater protection there must be against recurrence. If this thought is carried to its logical conclusion, removal of the entire stomach, and the consequent opportunity to remove the greatest amount of adjacent lymph glands and lymphatics, should be the ideal surgical procedure.

Total gastrectomy, although theoretically an ideal procedure, has one distinct drawback in that the loss of the entire stomach means the loss of the so-called intrinsic factor contained in gastric secretion and related to the maintenance of a normal number of red cells in the circulating blood. Anemia of the primary type has developed in some patients who have had the entire stomach removed. However, the administration of extract of liver seems to combat the anemia, and it should prolong life indefinitely, as it does in cases of ordinary primary

2. Ewing, J.: *Neoplastic Diseases*, ed. 4, Philadelphia, W. B. Saunders Company, 1940, p. 720.

anemia. Yet because in the recorded cases in which total gastrectomy was done the patient has never lived longer than four and a half years,³ there has been no opportunity to verify the efficacy of this treatment with certainty.

There are other practical obstacles to the more common performance of total gastrectomy. Operative mortality represents a major obstacle. Even subtotal gastrectomy as practiced by the average surgeon is attended by a high operative mortality. Livingston and Pack stated:

The present resection mortality in surgical centers performing large numbers of [subtotal] gastrectomies for cancer averages seventeen per cent while that for the casual surgeon or in clinics reporting small numbers of resections is found to average approximately thirty per cent. They stated further: No surgeon who is unqualified . . . has the moral right to operate on a patient with gastric carcinoma.

More frequent performance of total gastrectomy if attempted by the average surgeon would no doubt result in a staggeringly high mortality rate. The operative mortality would certainly be higher for total gastrectomy done by the trained gastric surgeon than for subtotal gastrectomy, but just how much higher unfortunately cannot be predicted. No large series of total gastrectomies has been recorded. In the few cases reported by any one surgeon the technic of the operation has varied with the surgeon and with the individual patient. While the operative mortality in the recorded cases has been relatively high, it must not be overlooked that in almost all the cases the surgical risk has been of the highest with such extensive tumors that every factor in the case was conducive to a high immediate mortality rate as well as to a high morbidity rate.

In 1937 Allen⁴ reported 15 cases of total gastrectomy; 5 were his own, and in 10 the operation was performed by eight of his associates. Eight of the 15 patients survived the operation. Of 7 patients operated on according to his finally evolved technic, 6 survived. This success was attained despite the factors previously mentioned as increasing the degree of risk in the patients, and it shows what may be accomplished by sound technic.

It therefore appears that the dangers attendant on total gastrectomy, both the possibility of anemia and the operative mortality, need not prove insurmountable. The control of anemia in the patients surviving the operation by the administration of extract of liver and the reduction

3. Walters, W.: Total Gastrectomy, in Eusterman, G. B., and Balfour, D. C.: *The Stomach and Duodenum*, Philadelphia, W. B. Saunders Company, 1935, pp. 628-635.

4. Allen, A. W.: Carcinoma of the Stomach, with Special Reference to Total Gastrectomy, *Tr. South. S. A.* **50**:165-175, 1937.

in the operative mortality by improvements already evident in the technic of the operation may permit indications for total gastrectomy accepted at present to be changed so that the operation will be performed in many cases of less than total and even only moderately extensive tumorous invasion of the stomach.

Before total gastrectomy can be justified as an acceptable clinical procedure, however, there must first be some basis for the belief that a better end result of total gastrectomy counterbalances the lower operative mortality rate of subtotal gastrectomy. Obviously, this cannot be proved from the figures now available, although the increase of radical operative procedures for malignant disease in other parts of the body has always improved the end results, and it seems reasonable to expect that operations on the stomach should be no exception. Many patients have lived longer after subtotal gastrectomy than any patient has lived after total gastrectomy. But no reported total gastrectomy has been attempted on a patient with less than practically total invasion of the stomach by tumor with the consequent probability of extension of the tumor beyond the limits of even total gastrectomy. In other words, in all instances of total gastrectomy for malignant disease of the stomach reported so far there has been little if any hope of cure, and the operations should be considered to have been essentially palliative procedures.

It was in an attempt to determine the end result of total gastrectomy and the chance of cure for patients with less than total invasion of the stomach by carcinoma that total gastrectomy was performed in 2 of the 4 personal cases reported hereinafter (cases 2 and 3).

The technic of the operation employed in the last 3 cases, in all of which the patients survived and were living and well at the time of writing, was evolved by the study of various technics employed in other recorded cases and by lessons learned through previous experience with subtotal gastrectomy and with total gastrectomy in case 1. No claim of originality is made. The postoperative convalescence of the last 3 patients suggests that the technic is sound.

THE OPERATION

Careful preoperative treatment, scrupulous operative technic and accurate postoperative treatment are all essential. Because a detailed account of the operation will be made the subject of another report, only a brief description will be given here.

Spinal anesthesia is believed to be most important in facilitating the operation. The technic employs anesthesia which usually persists for three or four hours. An upper midline incision is used. Total gastrectomy is accomplished by first completely mobilizing the entire stomach,

next severing the first portion of the duodenum, then gradually severing the lower end of the esophagus during the course of an anastomosis with the side of the first portion of the jejunum, which has been previously brought up through the transverse mesocolon. Because of the relation established between the jejunum and the mesocolon, entero-anastomosis does not seem necessary and is not used. Jejunostomy may be done, but it was not used in the cases hereinafter reported.

Aspiration at the site of gastrojejunostomy through a small nasal tube placed at the time of operation is constantly maintained for several days. Fluid balance is maintained by fluids and blood administered intravenously. Small amounts of fluids followed later by soft foods are given in eight or ten days, and within two weeks the patient readily tolerates a five meal type of diet. The meals must remain small for a time, but the jejunum eventually dilates so that regular meals are taken comfortably. Vitamins and possibly extract of liver should be given temporarily.

REPORT OF CASES

CASE 1.—W. C. G., a white man aged 55 years, was admitted to the University of Virginia Hospital Aug. 4, 1934. For eighteen months he had suffered with epigastric symptoms suggestive of duodenal or gastric ulcer or gastric carcinoma. During the last seven months he had lost 30 pounds (13.6 Kg.), and during the two weeks before admission his symptoms had become much more marked.

Physical examination revealed a palpable mass in the epigastrium, estimated at 4 cm. in diameter. Roentgen examination revealed carcinoma involving the lower two thirds of the stomach and an absence of six hour retention.

An operation was performed August 9. Spinal anesthesia induced with procaine hydrochloride, later supplemented with ether inhalation anesthesia, was employed. The operation lasted two hours and thirty minutes. An incision through the upper part of the right rectus muscle was made. Practically the entire stomach showed invasion by carcinoma, but no spread to adjacent structures or metastasis was evident. Total gastrectomy seemed necessary and feasible, and it was done. A postcolic esophagojejunal anastomosis was made, the technic of which varied from that employed in the other cases in several details now recognized as important. Nevertheless, the patient stood the operation well and was returned to his ward in excellent condition. The pathologic diagnosis was colloid carcinoma of the stomach without metastasis to the regional lymph nodes.

The postoperative convalescence was complicated by signs of pneumonic consolidation in the base of the left lung twenty-four hours after operation. The patient died of pneumonia four days after the operation. Necropsy confirmed pneumonia as the cause of death, for the peritoneum showed no more reaction than was to be expected after any gastric operation.

CASE 2.—L. L., a married white woman aged 48 years, entered the University of Virginia Hospital Jan. 8, 1939. During the preceding two years she had suffered periodically with symptoms typical of duodenal ulcer and had lost 35 pounds (15.9 Kg.). She had been under investigation and medical care in the outpatient department since Nov. 11, 1938. Roentgen examination of the stomach

had revealed a large gastric ulcer at the incisura angularis (fig. 1 *A*). Against advice, she deferred operation.

When she finally did enter the hospital, preparations for the operation were carefully carried out. On January 11, the operation was performed. Carcinoma affected only the lesser curvature of the stomach, though it involved that fairly extensively. There was no evidence of spread or metastasis of the tumor; and although extensive subtotal gastrectomy might have eradicated all grossly demonstrable tumor, it seemed to me that total gastrectomy offered a better prognosis. Therefore, the entire stomach was removed, according to the technic described previously. The operation occupied two hours and thirty minutes. The pathologic diagnosis was adenocarcinoma of the stomach with many features of colloid carcinoma. The lymph nodes were not involved.

The patient's postoperative convalescence was remarkably smooth, and her highest temperature was 100.4 F. by rectum. The nasal tube was removed nine days after operation. Fluids were being taken by mouth twelve days after operation, and soft foods were permitted two days later. She was discharged to her



Fig. 1 (case 2) —*A*, carcinoma of the stomach; *B*, esophagojejunal anastomosis and reservoir-like dilatation of the afferent and efferent loops of the jejunum eleven weeks after total gastrectomy.

home on the seventeenth day after the operation, able to get about freely and tolerating a five meal diet.

Her course has been followed for over two years since the operation at intervals of from six weeks to three months. Her most recent visit was April 10, 1941. As early as March 28, 1939, eleven weeks after the operation, roentgen examination revealed a perfectly functioning esophagojejunal stoma with the formation of a reservoir for food as a consequence of dilatation of both the afferent and the efferent loops (fig. 1 *B*). She has continued to have an excellent appetite and, except for an occasional burning sensation in the throat relieved by taking a pinch of bicarbonate of soda, she has had no discomfort or other symptoms of abnormality. On Nov. 2, 1939, she stated that she had enjoyed a lunch consisting of a bowl of soup, a plate of lima beans, two glasses of water and a large slice of custard pie. The same day, analysis of 24 cc. of material aspirated from the jejunal reservoir revealed no hydrochloric acid and total acids of only 10 degrees

Since the operation her weight has never returned to her original maximum though, except for minor fluctuations, it has been maintained at a constant level, about 15 pounds (6.8 Kg.) below her preoperative weight.

Careful study of her blood at frequent intervals has failed to demonstrate any important change. The hemoglobin content has not fallen below 70 per cent (Dare), and the lowest erythrocyte count has been 3,760,000. At that time, six months after operation, she was given some extract of liver and iron for a short time but has had no medication since then. At the time of her visit, Oct. 10, 1940, the hemoglobin was 80 per cent (Dare), and her erythrocyte count was 4,090,000. At the time of writing, more than two years after total gastrectomy, she appears to be well, healthy and free from any signs of recurrence or metastasis.

CASE 3.—A. S., a white man aged 38 years, entered the University of Virginia Hospital on Feb. 22, 1940, complaining of gastric symptoms of fourteen years' duration. Aggravation of the pain, nausea and vomiting had been troublesome during the last five months. In 1935 he had undergone an emergency operation

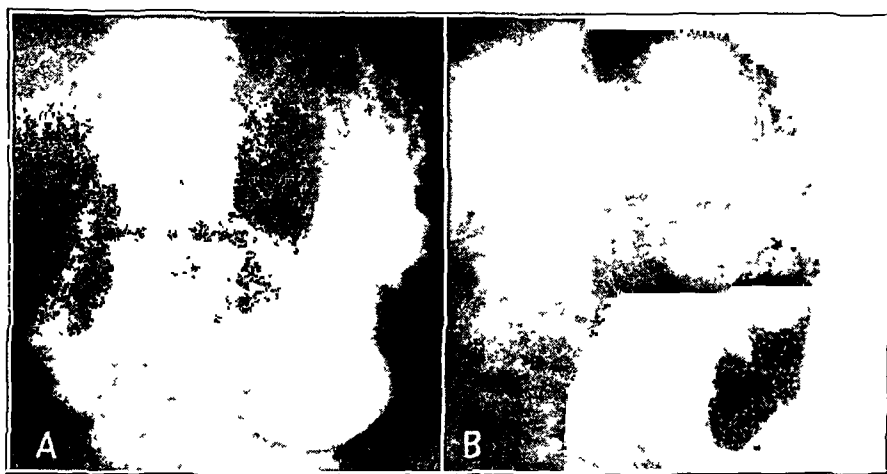


Fig. 2 (case 3).—*A*, carcinoma of the stomach; *B*, esophagojejunal anastomosis and reservoir-like dilatation of the afferent and efferent loops of the jejunum nine weeks after total gastrectomy.

elsewhere for simple closure of a perforated stomach ulcer. In 1937, again elsewhere, a posterior gastroenterostomy had been made. My investigation began in the medical outpatient department Feb. 14, 1940.

Except for sexual underdevelopment and evident loss of weight (20 pounds [9.1 Kg.]), physical examination showed him to be essentially normal. Roentgen examination of the stomach, however, revealed a functioning gastroenterostomy stoma and infiltration suggesting carcinoma in the lower half of the stomach (fig. 2 *A*).

The patient was carefully prepared for operation. On February 29 the operation was performed. Carcinoma involved practically the entire lower third of the stomach, but there was no sign of spread of the tumor or of metastasis. Total gastrectomy was decided on because of the relative youth of the patient (implying a poor prognosis) and the distortion of the stomach due to gastroenterostomy.

The jejunum was freed from the stomach, and the stoma in the jejunum was closed by suture. Total gastrectomy was performed according to the technic

already described, the esophagojejunal anastomosis being placed distal to the closed gastroenteric stoma in the jejunum. The operation consumed three hours, but the patient withstood it without difficulty. The pathologic diagnosis was colloid carcinoma of the stomach without involvement of the lymph nodes.

The patient's postoperative convalescence was entirely smooth; the highest temperature was 101 F. by rectum. The tube to the site of anastomosis in the esophagus was removed ten days after operation. Liquids were given by mouth the next day, and soft foods were allowed thirteen days after operation. He was discharged to his home on the seventeenth day after operation and tolerated a five meal diet without trouble.

His course since operation has been followed at regular intervals of six weeks and has been most satisfactory. He has had no complaint at any time except slight burning sensation in the throat controlled readily by taking a pinch of bicarbonate of soda. A good appetite and the ability to eat normal meals have been constant. Roentgen examination on May 2, two months after operation, revealed excellent function of the anastomosis and the formation of a reservoir for food by dilatation of both afferent and efferent loops (fig. 2 B). His weight rapidly increased to above his normal level and has been maintained. No anemia has been evident, but he has been given small amounts of extract of liver periodically. The last examination of the blood revealed a hemoglobin content of 80 per cent (Dare), and the erythrocytes numbered 4,300,000. On April 3, 1941, over one year after total gastrectomy, he was apparently well and healthy and showed no signs of recurrence or metastasis.

CASE 4.—S. A. C., a white man aged 61 years, entered the University of Virginia Hospital on Feb. 21, 1941, complaining of indigestion and pain in the epigastrium. The symptoms had started about a year before and at first had been intermittent. For the last two months, however, they had been almost constant, and he had vomited fairly frequently. Weight lost had amounted to about 30 pounds (13.6 Kg.).

Physical examination showed him to be essentially normal except for some enlargement of the prostate. Roentgen examination revealed a sclerosing carcinoma of the body of the stomach similar to linitis plastica. Only small areas of the stomach immediately adjacent to the pylorus and the esophagus seemed uninvaded.

After careful preoperative treatment for three days the patient was operated on February 25. The findings at operation confirmed the roentgen observations. Except for small cuffs of uninvaded tissue at the pylorus and the cardia, the entire stomach was like a tube of carcinoma. However, there was no sign of spread of the carcinoma beyond the stomach. Obviously, total gastrectomy was the only possible means of eradicating the grossly evident tumor.

Total gastrectomy was accomplished by the technic already described. The operation lasted two and a half hours. The pathologic diagnosis was diffuse carcinoma of the stomach, grade 4, with direct extension to the gastrohepatic and the gastrocolic omentum. The patient withstood the procedure well and had an entirely smooth and uneventful convalescence as far as the abdomen was concerned, though intercurrent prostatism necessitated the use of an indwelling catheter until the patient was allowed to get out of bed. The nasal tube was removed seven days after operation; the giving of liquids by mouth was started nine days after operation, and a day later soft foods were allowed. He was permitted to get out of bed on the twelfth postoperative day; a five meal diet was begun on the thirteenth day, and he went home on March 13, the sixteenth day, apparently in excellent condition. As in the other cases, plans have been made for follow-up examination at regular intervals. His condition was satisfactory at the time of his first follow-up visit on March 27.

SUMMARY AND CONCLUSIONS

At present total gastrectomy is performed on only a limited number of patients, only those with carcinomatous involvement of practically the entire stomach. In such cases the prognosis is practically hopeless, so that the operation must be regarded as having been only a palliative procedure. Consequently, most patients surviving the operation itself have died within a few months of recurrent or metastatic tumor, and no opportunity has been afforded for studying the end results of total gastrectomy from the standpoint of either remote physiologic effects or possible superiority over subtotal gastrectomy as a means of cure.

Because the end results of subtotal gastrectomy, even in the hands of the most experienced gastric surgeon, leave much to be desired and because recent developments in the technic of total gastrectomy appear to indicate the means of appreciably reducing the previously high mortality of patients subjected to the operation, it is suggested that the time may be ripe to attempt a real evaluation of total gastrectomy. A determination of the remote physiologic effects and the real end results in comparison with those of subtotal gastrectomy can be made only by performing total gastrectomy on patients with moderate tumorous invasion of the stomach and hence with a fair prospect of complete eradication of the tumor by surgical intervention. It seems reasonable to believe that the operative mortality can be lowered and that the end results will be improved to a point that may justify the use of total gastrectomy in many more cases than it is at present employed.

A technic for total gastrectomy has been described. The cases of 4 patients subjected to operation have been reported. In the first case the patient was not operated on by the described technic, and for this or some other reason he died of pneumonia early in the course of his convalescence. The other 3 patients had a most uneventful and smooth convalescence and at the time of writing are still alive and well—one, over two years after operation; another, over one year after operation, and the last, a few weeks after leaving the hospital. The patients in cases 2 and 3 had only moderately extensive carcinoma of the stomach and would ordinarily have been treated by subtotal gastrectomy. They were subjected to total gastrectomy in an attempt to begin an evaluation of the end results of total gastrectomy on patients for whom more radical surgical treatment might offer a better outlook for cure.

ASEPTIC NECROSIS AND BONE DRILLING

ERNST BERGMANN, M.D.

AND

ARTHUR KRIDA, M.D.

NEW YORK

Bone drilling as a therapeutic procedure is not altogether modern. About a hundred years ago Daniel Brainard,¹ a professor of surgery in Chicago, experimented successfully with subcutaneous bone drilling in animals. This led him to employ it in treating pseudarthrosis in human beings. Brainard recorded his investigations in an elaborate study which he dedicated to no less a person than the chief surgeon of Napoleon, Larrey, who had assisted him with material and experience. In Ollier's comprehensive book,² bone drilling is plainly referred to as "méthode Brainard." For all this, the procedure lapsed into oblivion.

About ten years ago the method was rediscovered and during the last decade has become a recognized means of treating delayed formation of callus and certain forms of pseudarthrosis. It seems obvious now that bone drilling with the consequent freshening of the bone, the formation of hematoma and the production of small detached and necrotic particles of bone should stimulate the formation of new bone.

Equally well conceived and borne out by practical results is the procedure of drilling in cases of slipping of the upper epiphysis of the femur. It brings about premature ossification of the epiphysial disk and thus prevents further progress of the deformity.

Treatment by bone drilling, however, has been extended to other conditions in which the theoretic foundation is less clear, for instance, to osteoarthritis. Yet, as a matter of fact, we have had occasion to observe that there is a distinct decrease of pain for some time after drilling of arthritic hip joints.

Finally, this form of treatment has been recommended for Perthes' disease and other forms of aseptic bone necrosis.³ It is particularly

From the Orthopedic Service of Bellevue Hospital.

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1. Brainard, D.: *Mémoire sur le traitement des fractures non réunies et des difformités des os*, Paris, J. B. Baillière, 1854.

2. Ollier, L.: *Traité expérimental et clinique de la régénération des os et de la production artificielle du tissu osseux*, Paris, V. Masson & fils, 1867.

3. Bozsán, E. J.: A New Treatment of Intracapsular Fractures of Neck of Femur and Calvé—Legg-Perthes' Disease, *J. Bone & Joint Surg.* **14**:884, 1932; **16**:75, 1934.

difficult to judge the influence of drilling on aseptic bone necrosis, for regardless of the type of treatment the subjective findings are usually insignificant, the healing time varies rather widely, and, above all, the stages of pathologic development seem to follow a definite course. It may be noted that the pathologic peculiarities of aseptic bone necrosis have not generally been given much emphasis. However, it is against

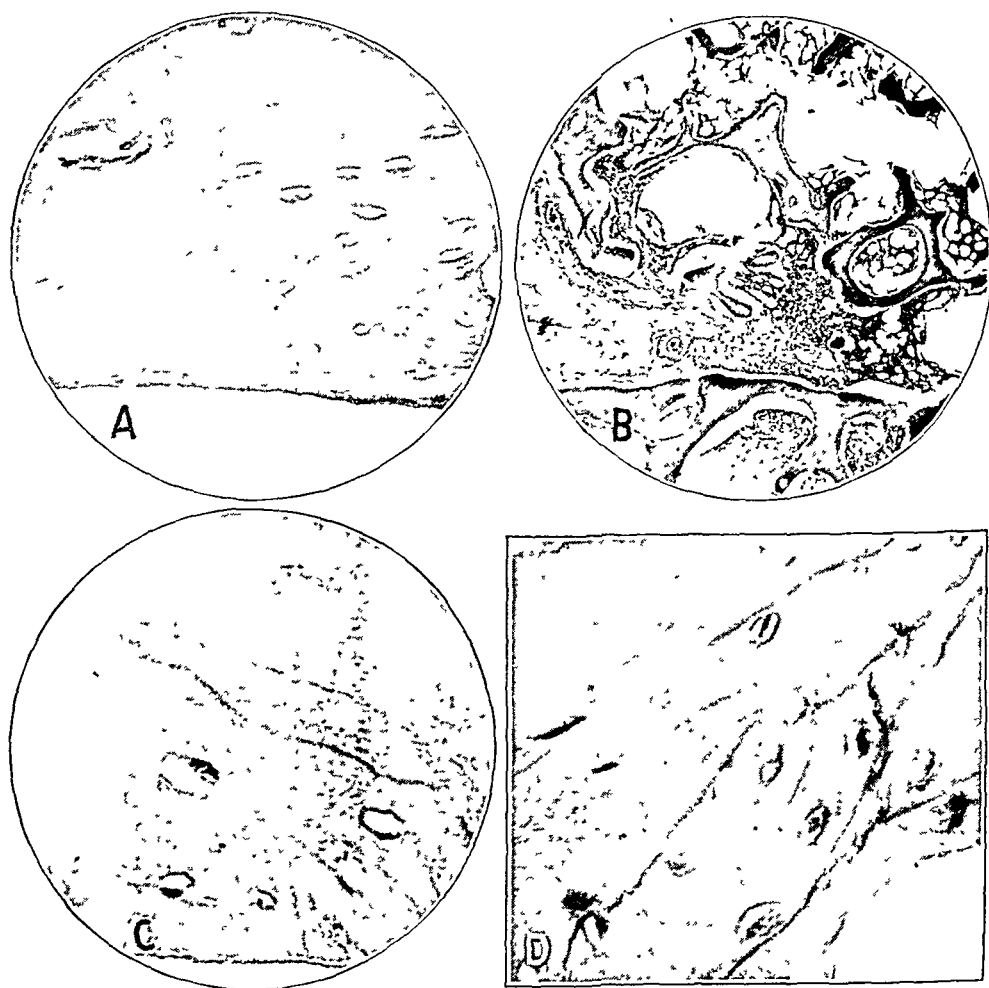


Fig. 1.—*A*, longitudinal section of a fibula of a dog two weeks after transplantation; the nuclei have disintegrated, leaving empty holes in the bony substance. *B*, lower third, invasion by fibrous tissue and blood vessels and formation of new bone; upper part, necrotic trabeculae and spaces filled with debris. *C*, newly built living bone demarcated from the dead lamella by a cement line. *D*, newly laid bone in an irregular arrangement (mosaic structure).

just this background that one must view the possible effect of drilling. The essential pathologic features will therefore be briefly reviewed.

It is only recently that physicians have come to know anything of this form of bone necrosis. Experimentation with bone transplants furnished

the initiative. Since Ollier's fundamental experiments, the superiority of autoplasmic osteoperiosteal grafts over other forms of bone transplants has been established. The practical application of the findings in that experimentation was advanced particularly by the work of Albee. While Ollier and his contemporaries believed in the survival of the transplant,

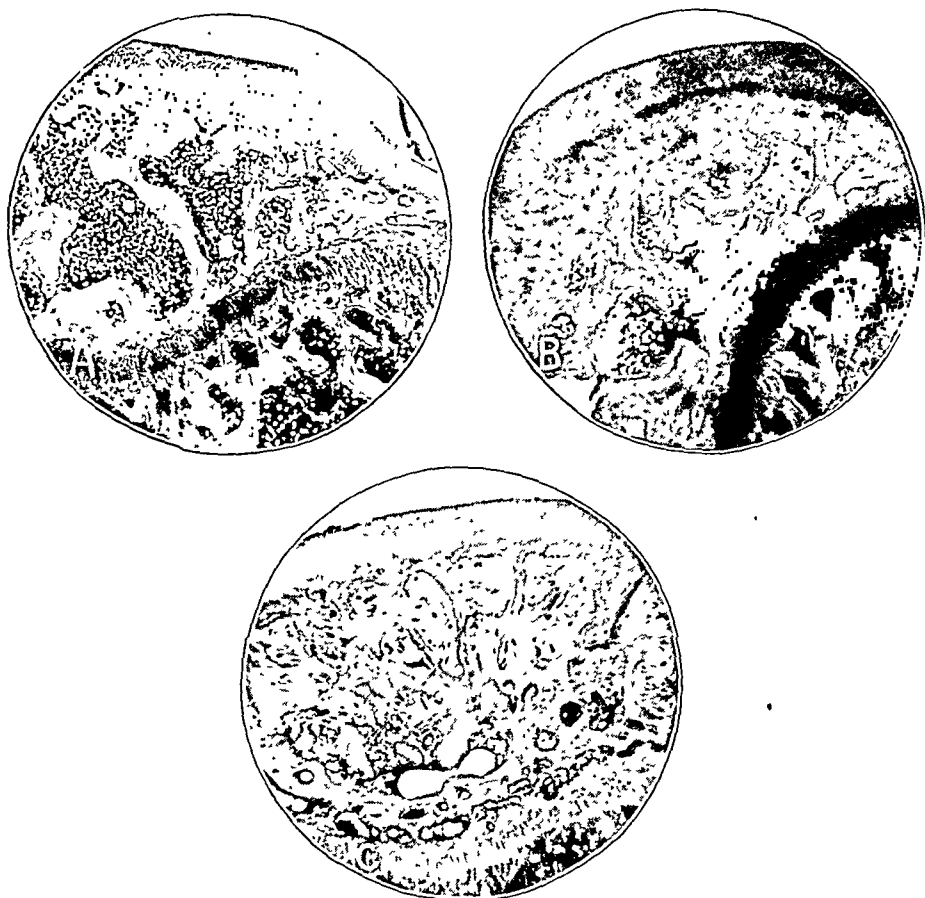


Fig. 2.—*A*, normal upper femoral epiphysis of an adolescent rabbit. *B*, head of the femur of the adolescent rabbit about two months after circumcission of the capsule of the hip joint and severance of the ligamentum teres femoris; the epiphysial bone and marrow are necrotic; the bone trabeculae are pressed together, particularly in the subchondral region; the joint cartilage is alive and thickened because endochondral ossification is suspended. *C*, the head of a femur of another rabbit after the same time and procedure; invasion of the fibrous medulla is already present throughout the epiphysis; replacement of bone is under way, absorption prevailing; the epiphysis is flattened.

Barth⁴ was able to demonstrate that bone grafts could turn necrotic and yet heal in. Barth's findings were in large part proved correct and, in the last analysis, were the foundation on which rested subsequent

4. Barth, A.: Ueber Osteoplastik, Arch. f. klin. Chir. 86:859, 1908.

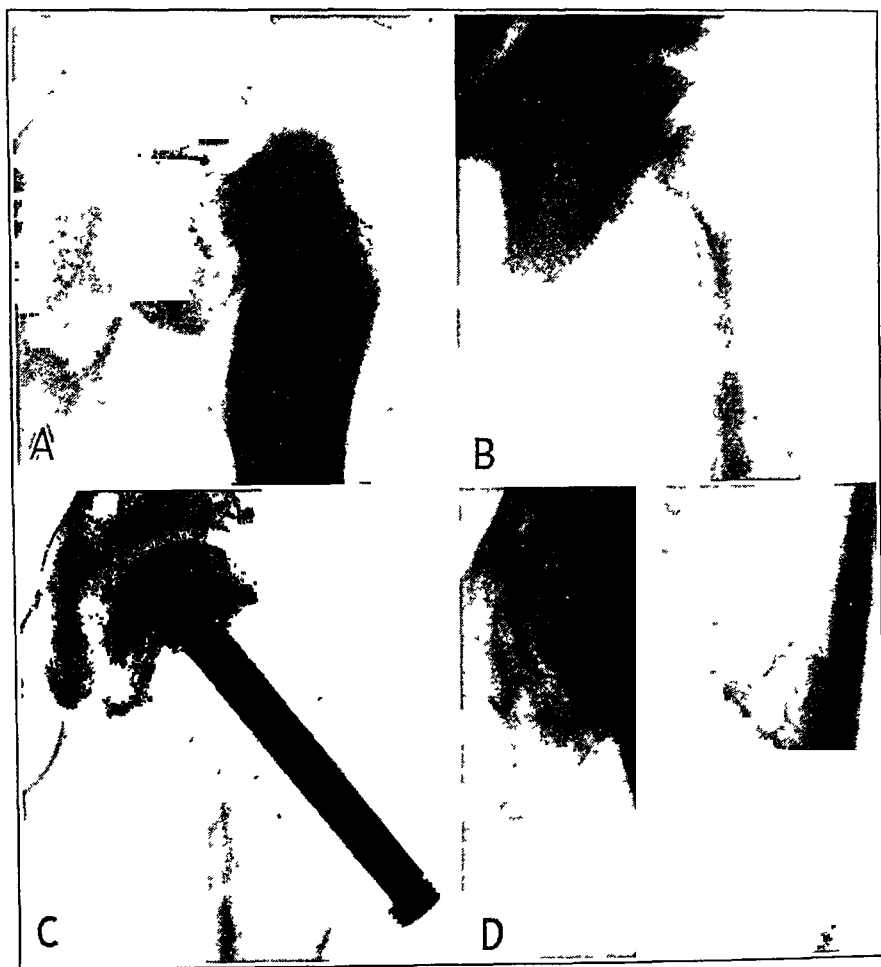


Fig. 3—The correlation of the pathologic state of a bone with the roentgen observations is illustrated in this figure and in figure 4. *A*, recent epiphyseal separation in a 12 year old girl. Roentgenologically it cannot as yet be said whether there is necrosis of the head of the femur. *B* shows that after traction for three weeks the head has retained its original density and that the shaft is markedly decalcified as a result of disuse; the same disuse has failed to produce any changes in the head, and it may therefore be assumed that circulation to the head is interrupted. *C* shows that the closed reduction has been completed and that subsequent nailing has been done to maintain proper alinement; the contrast in density is pronounced. *D*, taken three months after nailing, indicates that function has been resumed and that the density of the shaft has come back to normal; on the other hand, the head has begun to lose some of its density, and this implies that restitution is on its way; at the same time, it may be seen that necrosis of the head does not necessarily interfere with bone union.

investigations by Axhausen,⁵ Phemister⁶ and others, who showed the important role played by aseptic necrosis in bone disease apart from that due to transplantation.



Fig. 4.—*A*, taken six months after operation, shows that the density and the structure of the head also have returned to normal; the process of healing seems to be finished. *B*, taken a year after nailing, shows that pathologic fracture and collapse of the head of the femur have occurred, apparently before bony substitution was completed. *C* shows that the nail, no longer serving a useful purpose, has been removed. The picture, if one did not know the history, would suggest Perthes' disease in the stage of fragmentation and condensation.

5. Axhausen, G.: Die histologischen und klinischen Gesetze der freien Osteoplastik auf Grund von Thierversuchen, *Arch. f. klin. Chir.* **88**:23, 1908. Axhausen, G.; and Bergmann, E.: Die Ernährungsunterbrechungen am Knochen, in Henke, F., and Lubarsch, O.: *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1937, vol. 9, pt. 3.

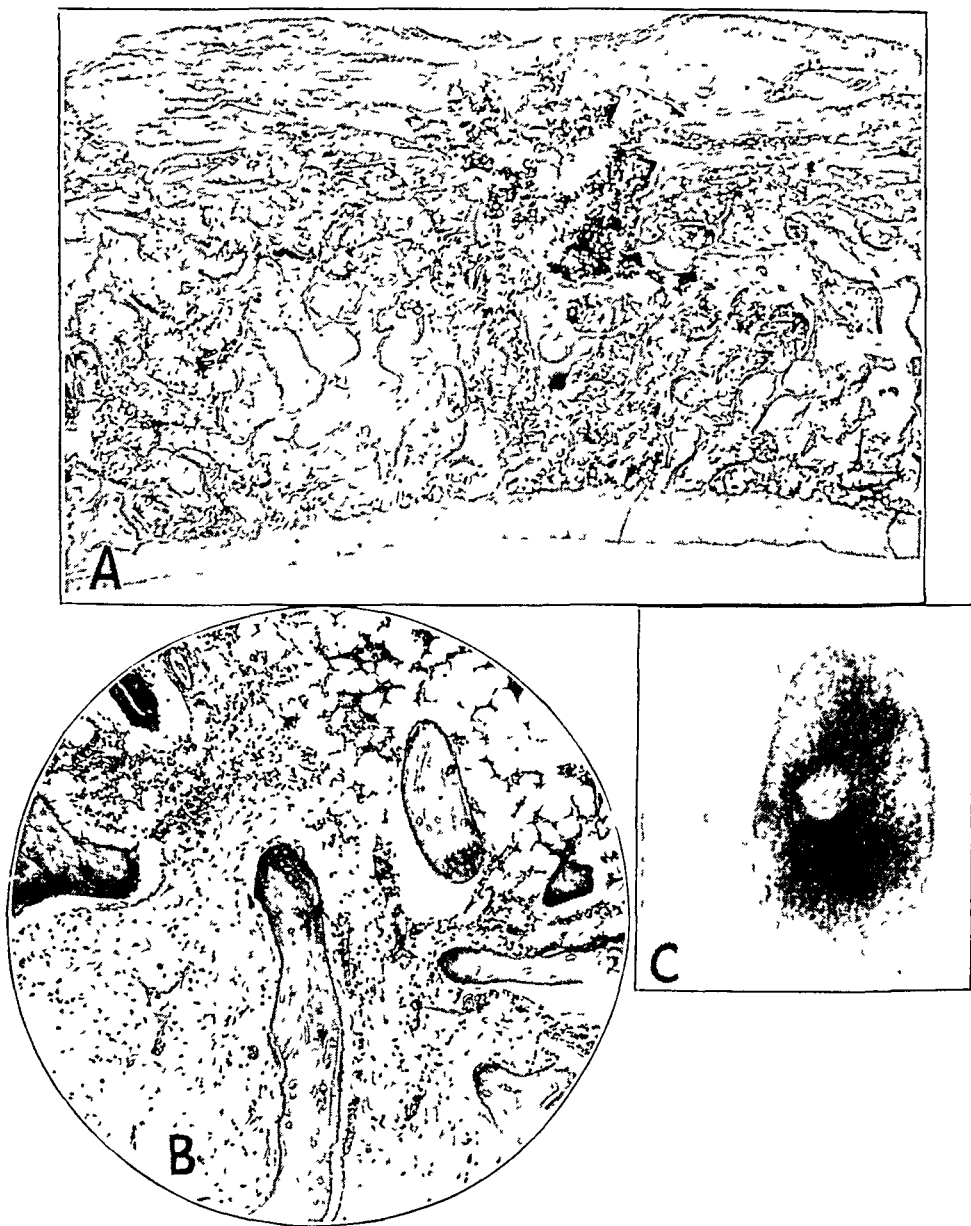


Fig. 5.—*A*, photomicrograph of a patella of a dog two months after drilling; the beginning of fibrous invasion is shown in the lower left corner. *B*, photomicrograph of a higher magnification of the invaded region far away from the drill canal, showing capillaries and connective fibers pushing forward toward the dead medulla. *C*, roentgenogram showing that loss of density proceeds from the periphery and that the region of the drill hole has not yet been reached.

6. Phemister, D. B.: Changes in Bones and Joints Resulting from Interruption of Circulation, *Arch. Surg.* **41**:436 (Aug.) ; 1455 (Dec.) 1940; Repair of Bone in Presence of Aseptic Necrosis Resulting from Fractures, Transplantations, and Vascular Obstructions, *J. Bone & Joint Surg.* **12**:769, 1930; Aseptische Knochennekrose bei Fracturen, Transplantationen und Gefäßverschlüssen, *Ztschr. f. orthop. Chir.* **55**:161, 1931; Fractures of Neck of Femur, Dislocations of Hip, and Obscure Vascular Disturbances Producing Aseptic Necrosis of Head of Femur, *Surg., Gynec. & Obst.* **59**:415, 1934.

Information about the vital processes of bone can be ascertained only from microscopic sections. Roentgen and gross appearances, valuable though they may be, are subject to interpretation. To gross inspection, dry and crumbling marrow is indicative of necrosis of the surrounding

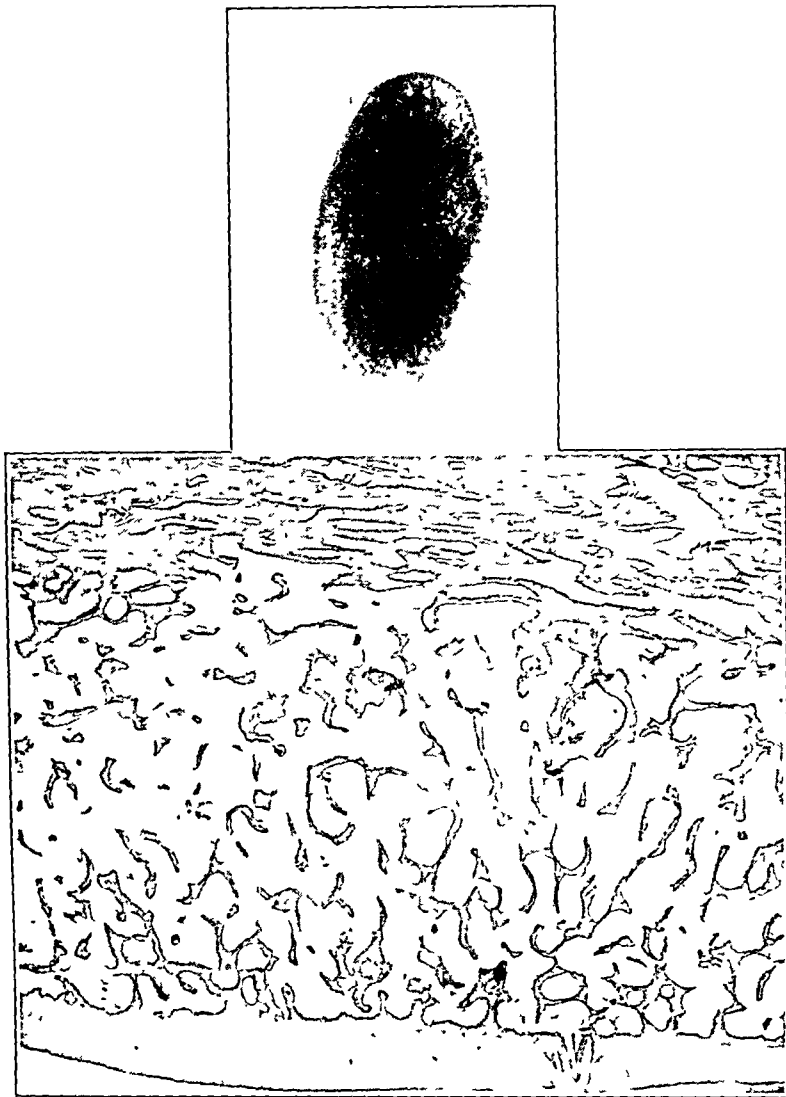


Fig. 6.—Roentgenogram and photomicrograph of the other (undrilled) patella of the dog in figure 5, showing that reorganization has not yet begun on this side; there is moderate production of bone at the lower end of the patella, apparently starting from surviving periosteum.

bone; in the roentgenogram the dead bone usually retains its original density in contrast to the adjacent living bone, which sooner or later shows signs of atrophy. Even microscopic observations, in view of the physical properties of bone tissue, require cautious evaluation.

Characteristic of bone necrosis is the failure of the nuclei to stain. However, interruption of the blood supply is not immediately followed by noticeable changes. At the end of the first week the nuclei may not be visibly impaired. This indifferent stage is followed by another stage

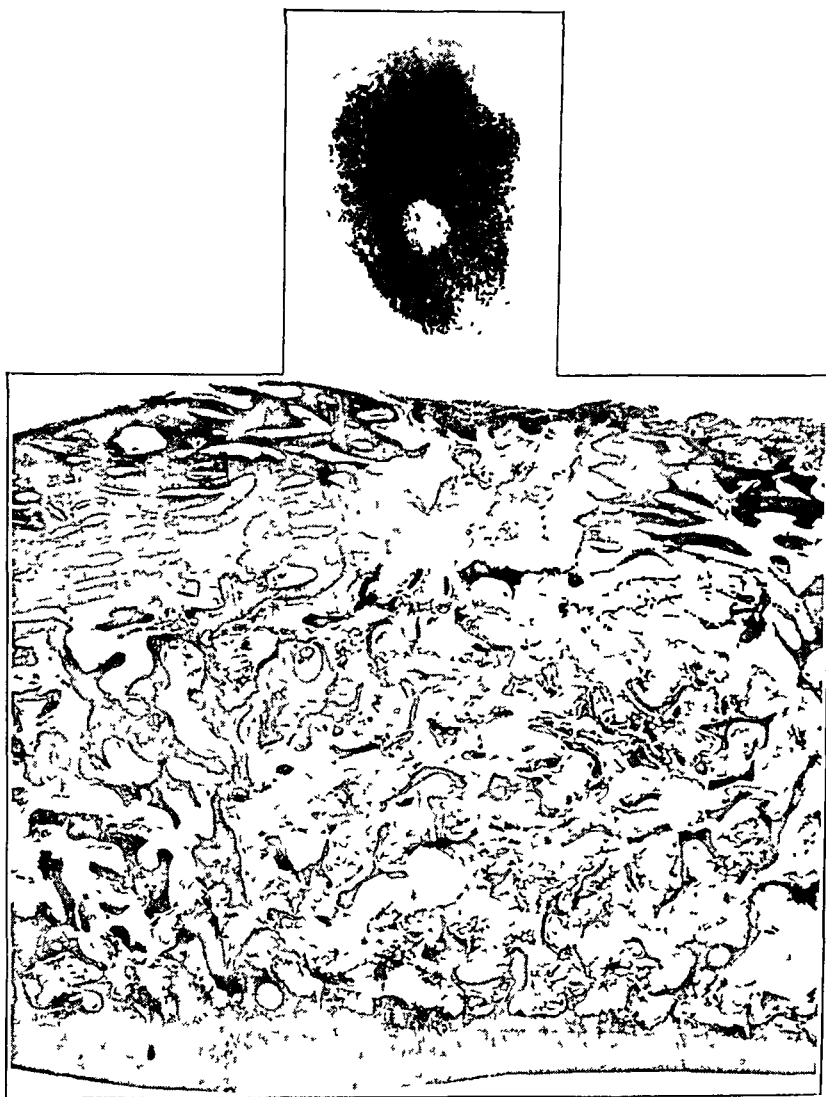


Fig. 7.—Roentgenogram and photomicrograph of the drilled patella of the dog in figures 5 and 6 after three months. As far as the process of repair is concerned, there is practically no difference between this and the undrilled side, shown in figure 8. In both this and the undrilled patella atrophy began at the periphery. There were no changes of density or structure around the drill canal.

in which pyknosis occurs. The cells may remain in this stage for some time. In the center of the necrotic areas, shrunken deeply stained nuclei may be observed for many months. However, this should not lead one

to believe that the bone has in part survived; this mistake is met with here and there in the literature. Then follows a third stage in which the nuclei disintegrate, leaving empty spaces in the bony substance which indicate their former places. Cells of the periosteum and the medulla

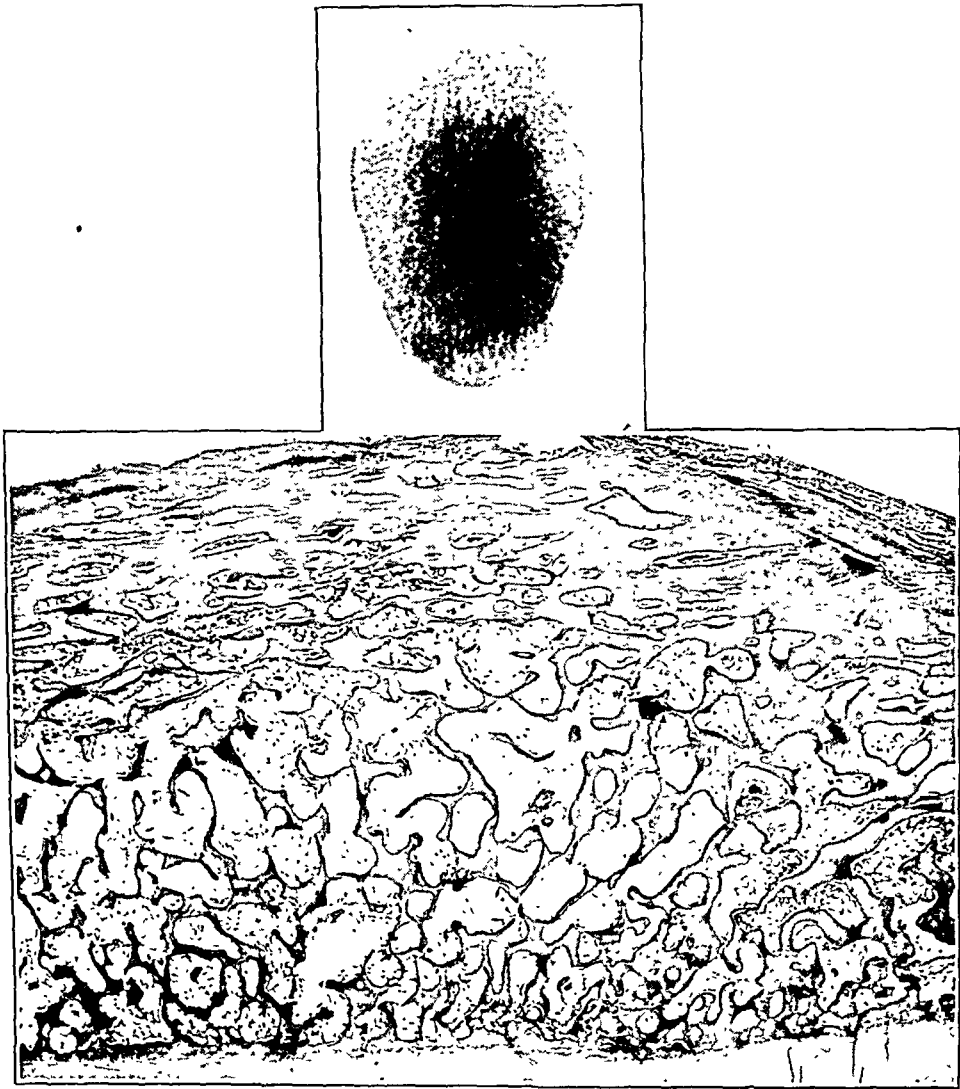


Fig. 8.—Roentgenogram and photomicrograph of the undrilled patella of the dog in figures 5, 6 and 7 after three months. From the roentgenogram it is evident that the bone has still retained more of its original density, indicating the slowness of restitution; this may have been due to the large size and the thickness of these knee caps. Apparently the undrilled side was the farther progressed.

seem less sensitive to the lack of blood supply, although in cases of epiphysial necrosis the marrow, in part or in whole, is dead. The joint cartilage, deriving its nutrition mainly from the synovial fluid, may or may not show signs of impairment.

Now, in contrast to what happens in osteomyelitic sequestration, in aseptic necrosis a process of restitution soon sets in with the ultimate objective of replacing the dead with new bone. To this end, capillaries and connective fibers originating from adjacent living marrow and

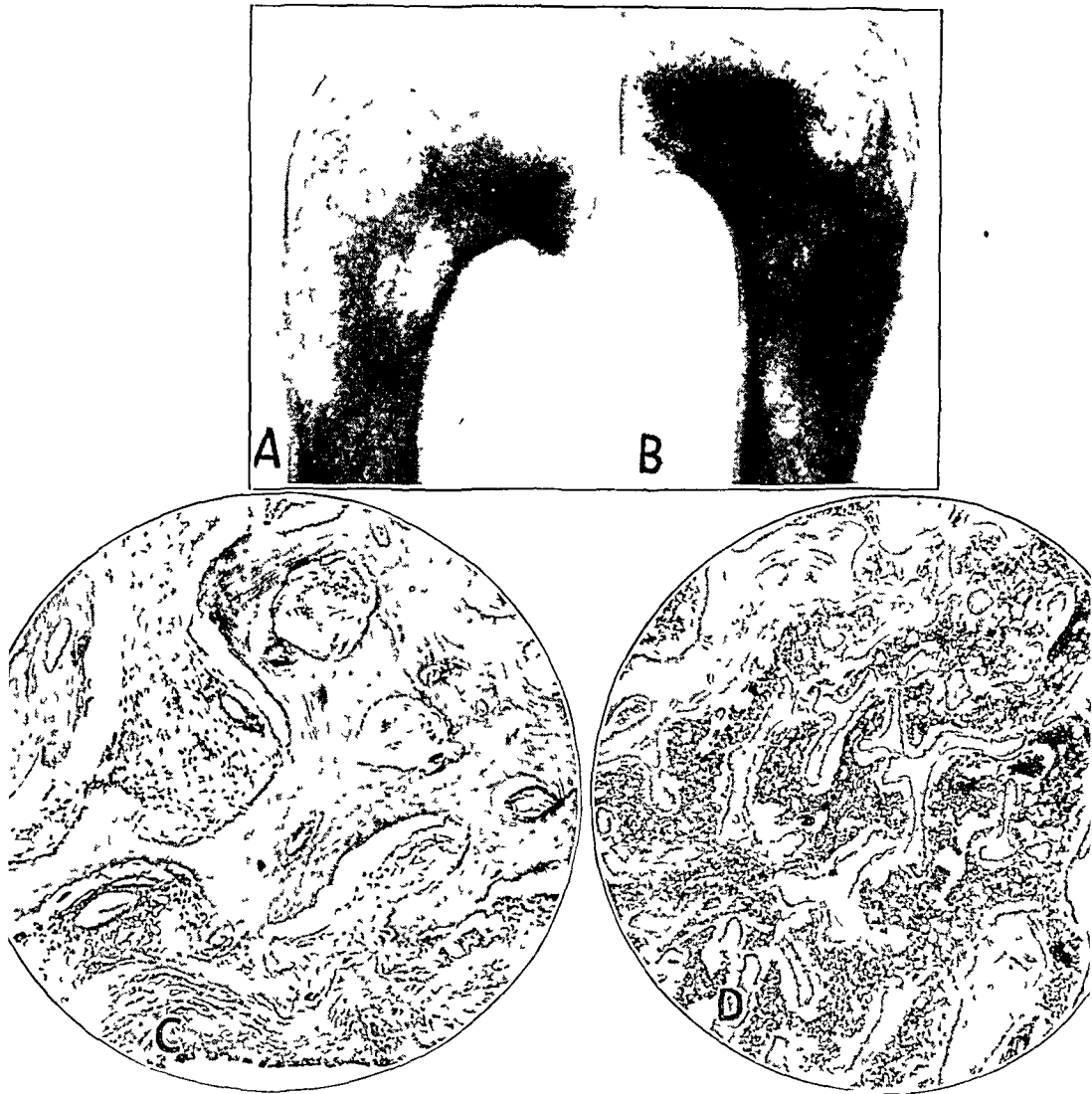


Fig. 9.—*A*, roentgenogram of the undrilled head of a femur of a dog two months after operation; the changes in density are more outspoken on this side. *B*, roentgenogram of the drilled head of the other femur; there is no indication of atrophy starting around the drill canal. *C*, photomicrograph of a section of the undrilled head; invasion by the vessels and the connective fibers starts from the periosteal cover of the neck of the femur, where it meets the joint cartilage. *D*, photomicrograph of a section of the drilled head; fragments of dead substantia spongiosa may be seen within the drill canal; the spaces are filled with debris from dead marrow cells and disintegrated blood.



Fig. 10.—*A*, roentgenogram of the head of a femur of a dog eight months after intracapsular fracture and drilling, showing that the subchondral necrotic area is less dense than normal, while the region of bony replacement is condensed beyond normal owing to an increase in the number and the size of bone trabeculae with consequent reduction of the spaces in the medulla. *B*, photomicrograph of the same head. The fracture ended in fibrous union. About two thirds of the head had undergone reorganization. In this area the bone trabeculae were increased in number and size by the lively deposition of new bone. Abruptly beyond this regenerated area was a zone of complete necrosis of bone and marrow. The sharp contrast between the finished regeneration of the greater part of the head and the total necrosis of the rest, together with the absence of any zone of transition, may illustrate the arrest of revitalization described by Phemister.

periosteum start to invade the spaces of dead *substantia spongiosa*. This fibrous tissue may contain giant cells in considerable number. Normally, fibrous invasion soon spreads over the entire area of necrosis. There is reason to emphasize that at this stage the bone trabeculae are still dead. If such a revascularized area of necrosis is cut through, it will bleed, giving the erroneous impression that the bone is alive. In fact, this has misled Ollier and many others.

The next phase is characterized by the replacement of the bone tissue proper. The invading connective fibers, because of their origin, carry specific components for bone formation and absorption. As a rule, resorption outweighs temporarily the deposition of new bone. Hence, the roentgen picture changes from the original density to atrophy and less distinct structure.

Elimination of dead bone is brought about either by lacunar resorption (that is, through the activity of specific cells, osteoclasts) or by way of creeping substitution. In the latter process, the new bone itself is thought to dissolve the necrotic one. Creeping replacement, long a matter of dispute, is still poorly understood in its exact details.

In general, newly formed bone is sharply demarcated from the old by a cement line. Also regarded as characteristic of new bone is its mosaic structure, in other words, the irregular arrangement of its lamellas. Later the structure adjusts itself to the requirements of function.

The normal course of restoration thus far outlined could be completed within several months if undisturbed. Usually, however, there are disturbances which greatly delay the process of repair. The dead epiphysis, since it is less resistant, may crumble through physical stress, form pathologic fractures and collapse; this condition is present when roentgen examination reveals fragmentation and condensation. The small fragments, pressed by weight bearing into a solid mass of bone sand, may form a barrier against the invading tissue and cause retardation of the revitalizing process. The course of restoration may even be entirely interrupted at any stage, as it is in cases of osteochondritis dissecans. As in this condition, so in cases of fracture of the neck of the femur a wedge-shaped piece of dead bone may separate from the upper quadrant of the head of the femur; however, this does not occur until the fracture has healed, for apparently only then do the mechanics of weight bearing come fully into play. Strangely, this separation may occur after two years or more, at a time, therefore, when all necrotic bone should long since have been replaced. This seems to indicate that the capacity of repair may be exhausted before attaining its aim, particularly in old age, as Phemister has pointed out.

It would be logical to expect the separation to take place at a line of demarcation between a living and a dead zone. In fact, however, it usually occurs within the dead area. Incidentally, this occurs also in cases of osteomyelitis, in which the sequestrum is often only part of the necrosis.

Such in short is bone disease as it ensues from interruption of blood supply under aseptic conditions. Obviously, the different phases of reorganization follow rather definite rules. It is hard to conceive that drilling should bring about a fundamental change, though it may speed up the natural course.

To arrive at a more precise understanding of the effect of drilling it seemed worth while to check on this question by experimentation. In earlier experiments one of us (E. B.)⁷ had produced aseptic bone necrosis by circumcision of the joint capsule of the hip and simultaneous severance of the ligamentum teres femoris. The necrosis corresponded in extent to that found in cases of intracapsular fracture of the neck of the femur. Another method of producing aseptic necrosis is to ligate all soft tissues about the patella. Experiments along these lines were resumed in the Laboratories of Experimental Surgery, of which Dr. Frank W. Co-Tui is director. The intent was to produce bilateral necrosis of the head of the femur or the patella and to drill one side and leave the other to its natural course. Fourteen animals, mostly grown-up dogs, were used, but because of death, infection or failure to show necrosis, 6 animals were eliminated.

The results of the experiments carried out with the 8 remaining animals may be summarized briefly as follows: Specimens were examined after two, three and eight months. Differences between the drilled and the undrilled side were but slight whether expressed in terms of microscopic or of roentgen observation. In 1 instance, though, revascularization was fairly advanced in the drilled bone, while the bone of the other side still remained almost inactive. However, fibrous invasion began some distance from the drill hole at a point where the periosteum and the joint cartilage met. In later stages no distinct signs were observed in the way of a more advanced restitution of one side. The revitalizing process proceeded mainly from the periosteum-covered surface. The drill canal and its immediate surroundings gave no conclusive evidence of initial fibrous invasion.

7. Bergmann, E.: Theoretisches, Klinisches und Experimentelles zur Frage der aseptische Knochennekrosen, *Deutsche Ztschr. f. Chir.* **206**:12, 1927; Der Anteil der einzelnen Wachstumzonen am Längenwachstum der Knochen, *ibid.* **213**:303, 1929; Osteochondritis dissecans des Hüftgelenks, *ibid.* **217**:400, 1929; Ueber das Längenwachstum der Knochen, *ibid.* **233**:149, 1931; Spätschäden nach geheilten Schenkelhalsbrüchen, *ibid.* **245**:496, 1935.

The nature of our experiments and observations call for cautious interpretation. It may be stated that drilling perhaps facilitates revascularization. However, we were unable to demonstrate changes significant enough to permit the recommendation of drilling as a useful therapeutic measure in cases of aseptic necrosis of bone.

Practical considerations make us hesitate to recommend drilling in cases of Perthes' disease, since it brings about premature closure of the epiphysis. This fact is of less significance in cases of slipping of the epiphysis because this condition occurs in adolescents. In cases of Perthes' disease, a condition which occurs between the ages of 5 and 9 years, drilling is more likely to cause shortening.

INCONSTANT SYMPATHETIC NEURAL PATHWAYS

THEIR RELATION TO SYMPATHETIC DENERVATION OF THE UPPER EXTREMITY

HOMER D. KIRGIS, PH.D.

AND

ALBERT KUNTZ, M.D., PH.D.

ST. LOUIS

The sympathetic innervation of the upper extremity is derived mainly from the cervicothoracic and middle cervical sympathetic trunk ganglions via gray communicating rami which join the lower cervical nerves from the fifth to the eighth and the first thoracic nerve. The inconstant intrathoracic ramus of the second thoracic nerve which joins the first conveys sympathetic fibers arising in the second thoracic and possibly lower ganglions of the sympathetic trunk into the brachial plexus (Kuntz).¹ In consequence of this finding, operative procedures for the sympathetic denervation of the upper extremity have generally been modified to include extirpation of the second thoracic segment of the sympathetic trunk, with the inferior cervical and first thoracic segments. This operation, as usually carried out, interrupts all generally recognized sympathetic pathways into the upper extremity. In some instances it fails to effect complete functional sympathetic denervation of the extremity. The persistence of functionally intact sympathetic fibers in the upper extremity in certain cases after extirpation of the inferior cervical and first and second thoracic segments of the sympathetic trunk suggests that there exist in these cases other pathways than those commonly recognized through which sympathetic nerve impulses reach the upper extremity.

The operative procedure, as usually carried out, does not include removal of the middle cervical ganglions, but all preganglionic fibers which reach these ganglions via the white communicating rami of the first thoracic or lower spinal nerves are interrupted. These ganglions are consequently functionally eliminated unless certain preganglionic fibers reach them via the lower cervical nerves. The existence of pathways outside the sympathetic trunk through which sympathetic fibers

From the St. Louis University School of Medicine.

1. Kuntz, A.: Distribution of the Sympathetic Rami to the Brachial Plexus: Its Relation to Sympathectomy Affecting the Upper Extremity, *Arch. Surg.* **15**: 871-877 (Dec.) 1927.

arising at levels lower than the second thoracic segment may reach the brachial plexus is not precluded. In 1931 Adson² advanced the opinion that some fibers which join the cardiac plexus via the thoracic cardiac nerves may traverse this plexus and reach the upper extremity. In 1941, by an experimental anatomic study carried out on cats, Van Buskirk³ demonstrated that some of the fibers which enter the vertebral canal from sympathetic trunk ganglions at lower levels ascend in the sinuvertebral nerve and join the ventral roots of the lower cervical and first thoracic nerves, through which they may enter the upper extremity.

A contribution of sympathetic fibers to the upper extremity via the cardiac plexus has not been actually demonstrated. Those fibers which enter the upper extremity via recurrent rami from the nerves in the vertebral canal are probably not sufficiently numerous to account for the manifestation in certain cases of functionally intact sympathetic fibers in the extremity after sympathectomy. The present investigation has been undertaken to determine more accurately the sources of the sympathetic fibers which enter the upper extremity and the anatomic pathways through which they join the brachial plexus.

In pursuance of this investigation 44 cadavers, all of which were used in the dissecting room during the school year (1940-1941), have been examined. Complete dissections of the thoracic and cervical portions of both sympathetic trunks including their connections with the spinal nerves were carried out in every case. Early in this work, one of us (H. D. K.) discovered a ramus arising from the third thoracic nerve just distal to the junctions of the communicating rami with it and joining the second thoracic nerve at approximately the same distance from its communicating rami. The frequency with which this ramus is present was carefully noted. In some instances it was removed and prepared for microscopic study. Several of these rami obtained at autopsy also were prepared for microscopic study. Particular attention also has been given the connections of the eighth cervical nerve with the cervicothoracic and lower middle cervical ganglions, including microscopic study of the proximal communicating ramus of the eighth cervical nerve in some cases.

ANATOMIC DATA

The anatomic relations of the thoracic and cervical portions of the sympathetic trunks and the arrangement of the communicating rami in

2. Adson, A. W.: Cervicothoracic Ganglionectomy, Trunk Resection and Ramisectomy by the Posterior Intrathoracic Approach, *Am. J. Surg.* **11**:227-232, 1931.

3. Van Buskirk, C.: The Nerves in the Vertebral Canal and Their Relation to the Sympathetic Innervation of the Upper Extremities, *Arch. Surg.* **43**:427-432 (Sept.) 1941.

general conform to current textbook accounts. A discrete inferior cervical ganglion occurs only rarely. In most instances the inferior cervical and first thoracic ganglions are fused, giving rise to a cervicothoracic or stellate ganglion which is highly variable in size and form. This ganglion is commonly located in the interval between the eighth cervical and first thoracic nerves and is usually connected with the first thoracic nerve by two communicating rami, with the eighth cervical by two, with the seventh cervical by one and sometimes with the sixth cervical by one. A large ramus arising from the superior border of this ganglion and extending upward along the posterior aspect of the vertebral artery gives rise to branches which form the major portion of the plexus on this artery and to relatively small rami which join the seventh and sixth cervical nerves. The gray rami arising from the cervicothoracic ganglion which join the cervical and first thoracic nerves obviously include the major portion of the sympathetic fibers which enter the upper extremity.

According to current textbook accounts, the middle cervical ganglion is absent in a high percentage of cases. This statement evidently refers to the ganglion which, when present, is located about the level of the sixth cervical segment. A ganglion located approximately at this level was present bilaterally in 13 and unilaterally in 2 of the 44 cadavers examined. This ganglion has been designated by Axford⁴ as the high type of middle cervical ganglion. It usually appears as a well defined enlargement on the cervical sympathetic trunk, from which communicating rami join the sixth and fifth and sometimes the fourth and seventh cervical nerves.

In all the cadavers examined there was present bilaterally another ganglion located on the medial side of the vertebral artery, approximately at the level of the eighth cervical nerve. It is relatively small in some cases but always clearly distinguishable (fig. 1). This ganglion has been designated by Axford as the low type of middle cervical ganglion. It is connected with the cervicothoracic ganglion by a large ramus which passes behind the vertebral artery and usually by another smaller one which passes in front of this artery. In most cases it is also connected with the cervicothoracic ganglion through the ansa subclavia. Few communicating rami arising from this ganglion join the brachial plexus. Frequently such a ramus joins the sixth cervical nerve, and rarely one joins the fifth or seventh. In cases in which there is a white communicating ramus associated with the eighth cervical nerve, some of its fibers may pass directly to the low middle cervical ganglion.

4. Axford, M.: Some Observations on the Cervical Sympathetic in Man, *J. Anat.* 62:301-318, 1927.

The first sympathetic trunk ganglion below the cervicothoracic, i. e., the second thoracic ganglion, is located at the level of the second thoracic nerve. It is connected with this nerve by a white and a gray communicating ramus. This ganglion has a peculiarly significant relation to the sympathetic innervation of the upper extremity, since many fibers which join the second thoracic nerve through its gray communicating ramus traverse the intrathoracic ramus of this nerve, which

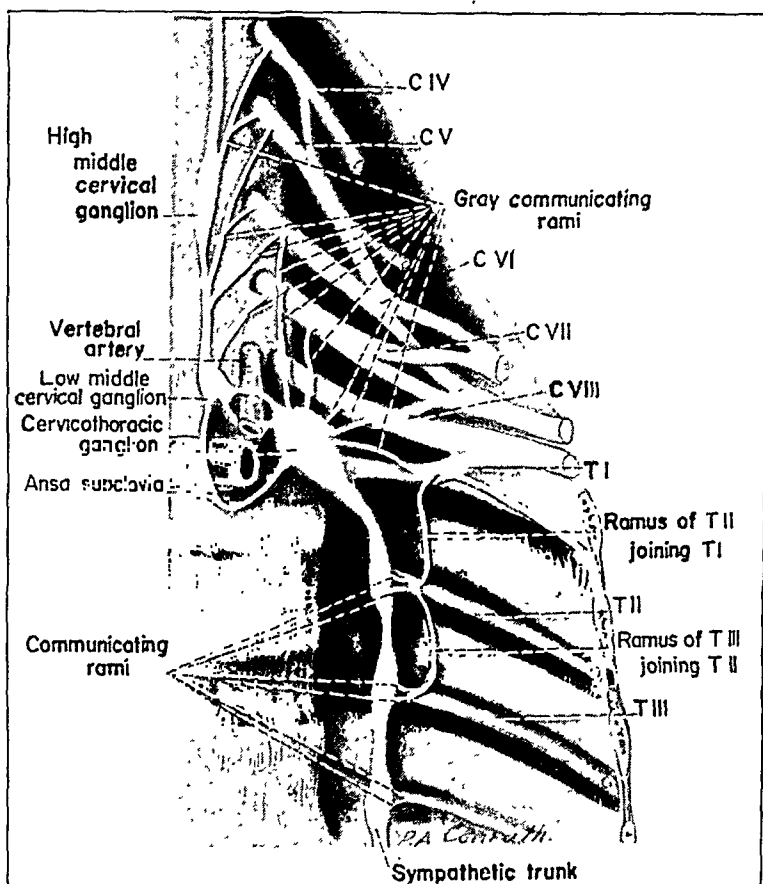


Fig. 1.—Drawing from a cadaver to illustrate anatomic relations of middle cervical, cervicothoracic and upper thoracic sympathetic trunk ganglia and rami from the second (*T II*) to the first thoracic nerve (*T I*) and from the third (*T III*) to the second thoracic nerve.

joins the first thoracic nerve, and enter the brachial plexus.¹ The intrathoracic ramus extending from the second to the first thoracic nerve was present bilaterally in 26 and unilaterally in 14 of the 44 cadavers examined. In the present series the percentage of cases in which this ramus could be demonstrated is somewhat higher than in the series studied earlier by Kuntz.

The second sympathetic trunk ganglion below the cervicothoracic, i. e., the third thoracic ganglion, is located at the level of the third thoracic nerve. It is connected with this nerve by a white and a gray communicating ramus.

A ramus arising from the third thoracic nerve just distal to the junctions of the communicating rami with this nerve and joining the second thoracic nerve (figs. 1 and 2) was demonstrated bilaterally in 15 and unilaterally in 18 of the 44 cadavers examined. In 6 of the remaining 11 cadavers, in which no direct communication between the third and second thoracic nerves could be demonstrated, a ramus arising from the third thoracic nerve either joined the second thoracic sympathetic ganglion or the sympathetic trunk just below this ganglion. In all cases in which the ramus arising from the third thoracic nerve joins the second, the junction occurs in proximity to the junction of the

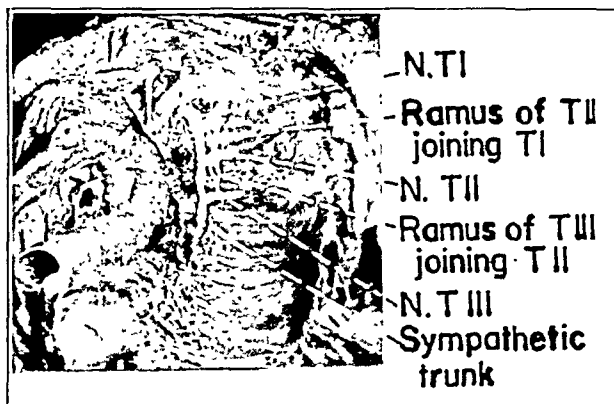


Fig. 2.—Photograph of a dissection showing the upper thoracic segments of the sympathetic trunk and rami from the second (*N. T II*) to the first thoracic nerve (*N. T I*) and from the third (*N. T III*) to the second thoracic nerve.

gray communicating ramus with the latter nerve or takes place directly with its gray communicating ramus and, consequently, in proximity to the origin of the ramus of the second thoracic nerve which joins the first. In some cases the ramus arising from the third thoracic nerve divides and joins the second at more than one point (fig. 2). In a few instances one branch could be traced directly into the ramus arising from the second thoracic nerve, which joins the first. The ramus in question, that arising from the third thoracic nerve, lies closely applied to the anterior surface of the third rib and the intercostal muscle and is embedded in the loose areolar connective tissue which lies in relation to the sympathetic trunk. If, instead of joining the second thoracic nerve, it joins the second thoracic sympathetic ganglion or the sympathetic trunk below the latter ganglion, it may be completely concealed by the connective tissue.



Fig. 3.—Photomicrograph of a transverse section of a ramus arising from the third thoracic nerve and joining the second. The broken lines indicate a peripheral area occupied by sympathetic fibers. Sympathetic fibers also are present in small groups among the somatic fibers.

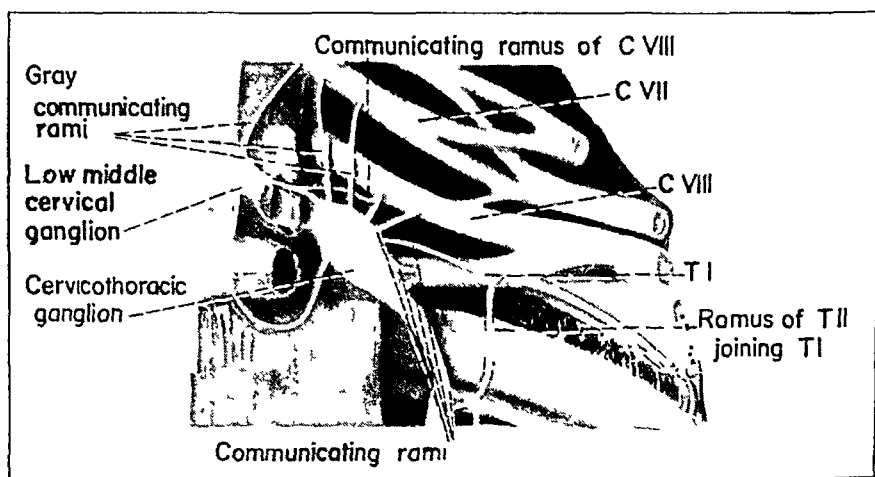


Fig. 4.—Drawing from a cadaver illustrating a communicating ramus of the eighth cervical nerve (*C VIII*) which joins both the cervicothoracic and the low middle cervical ganglia.

Microscopic study of transverse sections of the ramus extending from the third to the second thoracic nerve shows that the ramus includes unmyelinated fibers undoubtedly of sympathetic origin. Many of these are aggregated in a well defined bundle at the periphery of the ramus (fig. 3). Others occur in small groups of closely aggregated unmyelinated fibers between the larger myelinated somatic fibers. The percentage of sympathetic fibers in this ramus is greatly in excess of that normally present in the peripheral rami of the thoracic nerves.

In some cases one of the communicating rami which connects the cervicothoracic ganglion with the eighth cervical nerve bifurcates and sends one division into the low middle cervical ganglion (fig. 4). This ramus, as revealed by microscopic study of transverse sections, is made up mainly of unmyelinated fibers of small caliber which are undoubtedly postganglionic. In some instances small myelinated fibers are present among the unmyelinated ones. These myelinated fibers probably are mainly preganglionic fibers which in these cases emerge through the eighth cervical nerve. This communicating ramus, therefore, constitutes a pathway through which in certain cases some preganglionic fibers may reach the low cervical sympathetic ganglion without traversing the cervicothoracic ganglion.

CONCLUSIONS

The anatomic data set forth in the present paper show clearly that not all the sympathetic fibers which join the nerves of the brachial plexus (and which, consequently, may enter the upper extremity) traverse the gray communicating rami arising from the cervicothoracic and middle cervical ganglions. The intrathoracic ramus of the second thoracic nerve which joins the first (this ramus is present in a high percentage of cases) is recognized as a nerve through which sympathetic fibers arising in the second and lower thoracic sympathetic trunk ganglions enter the upper extremity. The ramus arising from the third thoracic nerve and joining the second, described in the present paper, occurs somewhat less frequently than the one arising from the second thoracic nerve and joining the first. It also includes a relatively high percentage of sympathetic fibers, many of which undoubtedly continue upward in the latter ramus and enter the ramus of the first thoracic nerve which joins the brachial plexus. A pathway is thus provided through which sympathetic fibers which leave the sympathetic trunk through the gray communicating ramus of the third thoracic nerve may enter the upper extremity without traversing gray communicating rami which join the first thoracic or cervical nerves. In order to interrupt this pathway by cervicothoracic sympathectomy it would be necessary to extend the operation downward to include extirpation of the third thoracic sympathetic trunk ganglion.

In view of the anatomic relations of the cervicothoracic and low middle cervical sympathetic ganglions, cervicothoracic sympathetic ganglionectomy does not necessarily involve extirpation of the low middle cervical ganglion. In certain cases, as observed in the present investigation, the communicating ramus of the eighth cervical nerve is connected with both the cervicothoracic and the low middle cervical ganglion. In some of these cases, this communicating ramus included some myelinated components which probably were preganglionic fibers which emerged from the spinal cord via the eighth cervical nerve. The continuity of the part of this ramus which joins the low middle cervical ganglion is not necessarily interrupted by extirpation of the cervicothoracic ganglion. In case it should be interrupted, any preganglionic fibers present might regenerate into the low middle cervical ganglion. Although the communicating ramus of the eighth cervical nerve probably conveys preganglionic fibers only in a low percentage of cases, it may in certain cases play a role in the sympathetic innervation of the upper extremity.

In view of all the anatomic data available, complete sympathetic denervation of the upper extremity by sympathetic ganglionectomy requires extirpation of the cervicothoracic and lower sympathetic trunk ganglions, including the second and third thoracic, in a relatively high percentage of cases. In certain cases, i. e., those in which the communicating ramus of the eighth cervical nerve includes preganglionic fibers, it may be necessary also to remove the low middle cervical ganglion.

WASH BASIN CONTAMINATION IN OPERATING ROOMS

J. K. POPPE, M.D.

Assistant in Surgical Bacteriology and Pathology, Yale University
School of Medicine
NEW HAVEN, CONN.

This bacteriologic investigation of contamination was occasioned by a recent change of solutions in the wash basins in the operating rooms of the New Haven Hospital. The weak bacteriostatic solution of iodine used previously was changed to sterile water in quantities of 1,000 cc. in each large shallow basin placed behind an operator, in which the operator washes off his gloves during the operative procedure. This change was made in the hope that discontinuance of the use of the iodine solution would decrease the dermatitis prevailing among the operating staff.

In a few cases a disinfectant, zephiran,¹ was put in the basins in a concentration of 1:5,000 in sterile water. This was done only when contamination of the basins during the operative procedure was most likely.

TECHNIC

The technic employed throughout these investigations was as follows: At the close of the operation 1 cc. of fluid was removed with a sterile pipet from either one or both wash basins. A pour plate was made with 10 cc. of melted beef infusion agar mixed with the 1 cc. portion of the fluid. In the instances in which zephiran was used this procedure gave a concentration of zephiran in the medium of 1:50,000.

Each culture was incubated at 37 C. for forty-eight hours, and then the colony counts were made and recorded. The following items were also noted: the name of the patient, the operator, the type of operation, the period over which the basins were exposed, whether the wound was considered contaminated and drained and, finally, whether any acute or gross infection was present one week after operation.

The cases hereinafter reported were selected at random so that examples of the main types of surgical procedure might be included. A large majority of the cases were selected because of the probability

1. Zephiran is alkyl dimethylbenzylammonium chloride. It is a cationic detergent having about the same consistency and physical properties as liquid soap, which is an anionic detergent.

that the fluid in the wash basins would become contaminated but only when such contamination would be important with respect to wound healing. For this reason all cases in which an abscess was drained and all cases in which rectal conditions were dealt with were eliminated. However, no results were rejected after a case was once selected.

CONTROL EXPERIMENTS

Control cultures to demonstrate the bacteriostatic action of zephiran were made by injecting single loopfuls of a beef broth culture of *Staphylococcus aureus* or *Streptococcus viridans* into tubes of melted agar. A series of tubes was used which contained dilutions of zephiran ranging from 1:10,000 to 1:100,000, as well as control tubes without

TABLE 1—*Bacteriologic Results of Control Cultures Made to Demonstrate the Bacteriostatic Action of Zephiran*

Dilution of Zephiran Used	Organisms	
	<i>Staphylococcus Aureus</i>	<i>Streptococcus Viridans</i>
1:10,000	0	0
1:20,000.	0	0
1:30,000.	0	0
1:40,000..	0	0
1:50,000..	0	0
1:60,000.	0	0
1:70,000..	0	0
1:80,000 .	Grade 1	0
1:90,000..	Grade 1	Grade 1
1:100,000.	Grade 1	Grade 1
Control tubes without zephiran	.	Grade 4

any zephiran. Growth in the control plates was measured from grade 1 (having less than five colonies per plate) to grade 4 (having innumerable colonies).

RESULTS

- (1) Cases in which cultures were made..... 22
- (2) Basins from which 1 cc samples were cultured.. .. 39
- (3) Cases in which viable bacteria were obtained from at least one basin.. 13
(56 per cent of all cases; 76 per cent of cases in which zephiran was not used)
- (4) Basins containing viable bacteria... .. 19 (49 per cent)
- (5) Cases in which zephiran was used in basins..... 5 (23 per cent)
- (6) Cases in which basins with zephiran yielded viable bacteria 0
- (7) Cases in which wound was considered contaminated and drained .. . 10 (45 per cent)
- (8) Basins used in cases in which drainage was done..... 18 (46 per cent)
- (9) Drainage cases in which basins contained viable bacteria.. 5 (50 per cent)
- (10) Drainage cases in which zephiran was used in basins . 3 (30 per cent)
- (11) Cases in which drainage was not done..... .. 12 (55 per cent)

- (12) Basins used in cases in which drainage was not done..... 21 (54 per cent)
- (13) Nondrainage cases in which basins contained viable bacteria 8 (36 per cent)
- (14) Nondrainage cases in which zephiran was used in basins.. 2 (17 per cent)
- (15) Longest period of exposure after which basin remained sterile without use of zephiran.....3½ hours
- (16) Controls 22
 Percentage of stock cultures sterilized by zephiran in 1: 50,000 solution 100
 Lowest dilution of zephiran in which bacteria grew..... 1: 80,000
- (17) Quantitative estimate of contamination:
 Cases in which viable bacteria were obtained from basins.. 13 (49 per cent)
 Cases in which colony count exceeded 5 per cubic centimeter 9 (41 per cent)
 Cases in which colony count exceeded 10 per cubic centimeter 4 (18 per cent)
 Cases in which colony count exceeded 40 per cubic centimeter 2 (9 per cent)
- (18) Predominating types of bacteria found in basins.....
Bacillus coli, Staphylococcus aureus, Bacillus proteus
- (19) Selected cases in which there was an acute wound infection or a breakdown of a drained wound..... 0

COMMENT

The discrepancy in several instances between the heavy infection of basins in some cases and the complete sterility in other apparently similar cases (zephiran being absent in both) may be accounted for by the fact that members of the senior surgical staff ordinarily rinse their hands in the basins a great many more times during an operation than members of the junior staff. A few of the basins, judging from the clean appearance of the water at the end of the operation and the sterility of the water, had not been used much, if at all, during the operative procedures. The same explanation applies to the fact that one basin in certain operations would be heavily contaminated and the other remain sterile. In these cases the operator usually remained on one side of the table, and the assistants did not use the other basin. This irregularity in the contamination of the two basins used in a single operation is the reason why the results are reported according to the number of cases rather than according to the number of contaminated basins.

The fact that some of the basins without zephiran remained sterile when exposed to the room air for as long as three and a half hours, apparently not used, serves to act as a control on the origin of the contamination. This is interpreted as evidence that the contamination

came primarily from the operator's hands and instruments rinsed in the basins and not from the air.

The fact is significant that 56 per cent of the total number of cases studied, or 76 per cent of the cases without antiseptic solution in the basins, showed sufficient numbers of viable bacteria, ranging from 1 to

TABLE 2.—*Data on Twenty-Two Cases in Which Cultures Were Made with Samples from the Fluid in the Wash Basins Used at Operation*

Case	Surgical Staff of Which Operator was Member	Operation	Time of Opera- tion, Hr.	Colony Count	Dirty Fluid in Basin	Zephiran 1:50,000, Used	Post- opera- tive Infection
1	Senior	Exploratory laparotomy.....	1	6	0	0	0
2	Senior	Resection of the colon.....	1½	0	0	+	0
3	Senior	Exploratory thoracotomy.....	1½	3	+	0	0*
4	Senior	Cholecystectomy.....	1½	6	+	0	0*
				18	+	0	
5	Junior	Excision of the submaxillary gland	1½	0	0	0	0
6	Junior	Leg amputation (guillotine).....	1	0			Wound left open
				20	+	0	
7	Senior	Spinal fusion.....	2½	8	0	0	0
				4		0	
8	Senior	Trephining.....	2	1	..	0	
				2	0	0	0
9	Junior	Cholecystotomy.....	1¾	0	+	+	0*
10	Senior	Craniotomy.....	3	0	0	0	0
			6	5		0	
				3		0	
11	Senior	Colectomy.....	4	0	+	+	0
12	Senior	Spinal fusion.....	3	0	0	+	0
				0		+	
13	Senior	Exploratory operation on the kid- ney	2	0	+	0	0
				0		0	
14	Junior	Colectomy.....	3½	0	+	0	0*
15	Senior	Lumbar sympathectomy.....	3	50	0	0	0
				0		0	
16	Junior	Cholecystectomy.....	1½	1	+	0	0*
				6		0	
17	Junior	Hernia.....	1½	0	0	0	0
				0		0	
18	Junior	Thyroidectomy.....	3½	6	0	0	0
					0	0	
19	Senior	Exploratory operation on the com- mon duct	2½	0	..	+	
				0	+	+	0
20	Junior	Hysterectomy.....	2	0	0	0	0
				2		0	
21	Senior	Exploratory laparotomy.....	2	1	0	0	0
				0		0	
22	Senior	Colectomy.....	4	40	..	0	
				13	+	0	0*

* Drainage was done.

50 organisms per cubic centimeter of fluid withdrawn from the wash basins, to be a definite hazard to aseptic technic and wound healing.

The complete absence of viable bacteria in all the cultured samples from the basins containing zephiran is in marked contrast to the contamination of 76 per cent of the basins without zephiran.

The absence of any badly infected wounds in the series is somewhat surprising in view of the high bacterial counts for some of the basins.

The fact that in 46 per cent of the cases the wound was drained probably eliminated some of the potential infections from contaminated basins. The basins in 36 per cent of the cases in which the wound was not drained were contaminated.

The cost (estimated at about \$10 a day) of supplying 400 cc. of the 1:1,000 stock solution of zephiran for each operation in a busy operating room is probably prohibitive. Some less expensive antiseptic which would be bactericidal in a dilution weak enough to eliminate dermatitis is almost essential to maintain a suitable aseptic technic.

Admittedly, the series of 22 cases studied is too small to permit any final conclusions as to the relation of contamination of the wash basins to the incidence of wound infection.

CONCLUSIONS

The wash basins in which the operators cleanse their hands in the operating room are frequently the most contaminated spots in the whole sterile setup.

The contaminated wash basins, used throughout the operation, act as a potential source of infection of the wound edges when these are closed and may account for the breakdown of a certain number of incisions.

An antiseptic solution should be placed in the wash basins in at least all cases in which a major operation is to be performed on the abdomen. The hands during intestinal manipulations in most of these cases become potential sources of infection but should be sterile while the abdominal wall is being closed. The antiseptic solution should be nonirritating to the operator's hands. It should be inexpensive, so that it can be used freely and so that the basins can be changed several times during a long operation. It should be used in sufficient concentration to be bactericidal in a few minutes in order to combat the moderate amount of contamination which is ordinarily introduced into the basins. Mere bacteriostatic action of an antiseptic in the basins is insufficient if the organism remains viable when cultured *in vivo*.

The average incision is apparently able to combat successfully a large amount of contamination without becoming infected. This is shown by the primary closure of all operative wounds except the drainage sites in all the cases reported (except a case in which the guillotine amputation was performed) despite relatively heavy contamination of the basins.

THE TWO STAGES OF BOWEL DISTENTION

A STUDY OF BOWEL INJURY BY DISTENTION AND ITS EFFECT ON THE VOLUME AND CONCENTRATION OF THE BLOOD

W. D. GATCH, M.D.

AND

J. S. BATTERSBY, M.D.

INDIANAPOLIS

What distending pressure will injure the bowel? All writers agree that injury done to the bowel by distention affects chiefly its circulation. The answer to this question should therefore be indicated by the fundamental relation between the volume of blood flowing through the wall of the bowel and the pressure within its lumen. This relation is that the volume of blood flowing through the wall of the bowel decreases as the intrainestinal pressure increases, until it becomes nothing when the intrainestinal pressure is equal to the systolic blood pressure.¹ A corollary to this is the fact that a continuous flow of blood ceases when the intrainestinal pressure exceeds the diastolic blood pressure. Then a flow through the blood capillaries occurs only during ventricular systole. Proof of the critical importance of the relation between the intrainestinal pressure and the diastolic blood pressure is that intes-

1. (a) Gatch, W. D.; Trusler, H. M., and Ayers, K. D.: *Effects of Gaseous Distention on Obstructed Bowel*, Arch. Surg. **14**:1215-1221 (June) 1927. (b) Dragstedt, C. A.; Lang, V. F., and Millet, R. F.: *The Relative Effects of Distention on Different Portions of the Intestine*, *ibid.* **18**:2257-2263 (June) 1929. (c) Dragstedt showed that the decrease in blood flow, which he recorded in percentages of the normal flow, is most marked in the duodenum and least marked in the colon. He gave an anatomic explanation for this based on the demonstration by Eisberg that from the duodenum to the colon the points at which the vasa recta pierce the muscularis of the bowel are situated farther and farther from the mesenteric border of the bowel. They are near the mesenteric border of the duodenum and in the amesenteric quadrants of the colon.

We doubt the validity of this explanation, because the impairment of the circulation is evidently due to compression of the bowel capillaries, and we cannot see how the points at which the vasa recta pierce the muscularis of the bowel can have any effect on this. The anatomic explanation we favor is that there is a gradual decrease in the thickness of the mucosa from the duodenum to the colon. The submucous coat of the bowel offers most of the resistance to distention, and the mucosa surrounded by it is compressed more by distention than is the muscularis. Therefore, the effect of distention will be most marked where the mucosa is thickest (i. e., in the duodenum) and least marked where the mucosa is thinnest (i. e., in the colon).

tinal function, as shown by the power of absorption, ceases when the intrainestinal pressure equals or exceeds the diastolic blood pressure.²

The blood flow through the intestinal wall depends not only on the intrainestinal pressure but also on the diastolic blood pressure. For example, when the diastolic blood pressure is 80 and the intrainestinal pressure 60 mm. of mercury, there will be a fairly large flow of blood. However, this flow will not be continuous if the diastolic blood pressure sinks to 60, as the pressure often does in patients with advanced obstruction. Then the pulse pressure also may be low, and the flow of blood will almost cease.

Few direct measurements of intrainestinal pressures have been made. Those recorded vary from 13 to 111 mm. of mercury.³ The facts are: (1) that except for extremely high pressures the intrainestinal pressure alone is no measure of the impairment of circulation; (2) that a pressure high enough to put the wall of the bowel under tension will decrease in the course of a few hours because of dilation of the bowel; (3) that the color of the wall of the bowel and its degree of tensity clearly show whether the pressure is injuring it.

Experiments show that a pressure great enough to cause tenseness of the wall of the bowel will slowly decrease as the bowel dilates and becomes flaccid; that a tense bowel has a greatly diminished blood flow; that a flaccid bowel has enough blood flow to keep it alive, though it suffers from congestion of blood in its capillaries. Thus dilation protects the bowel against high intraluminal pressure, provided the pressure does not increase step by step with the dilation.

These observations on the experimental animal are similar to those made at operation for obstruction of the bowel in man. We find clinically that the bowel for a variable distance proximal to an obstruction is always dilated. In some cases it is tense, dry and pale; in other cases it is flaccid, edematous and blue. Here also, the tense pale bowel is being injured, and the flaccid blue bowel is convalescing from injury. The significant pressure, that is, the pressure which damages the bowel, is the pressure within the tense pale bowel. We know by deduction and experiment that this must be near the diastolic blood

2. Gatch, W. D.; Owen, J. E., and Trusler, H. M.: The Effect of Distention of the Bowel upon Its Circulation and upon Absorption from Its Lumen, *West. J. Surg.* 40:161-170, 1932.

3. Stone, H. B., and Firor, W. M.: Absorption in Intestinal Obstruction: Intra-Intestine Pressure as a Factor, *Tr. South. S. A.* 37:173-184, 1924. Sperling, L.; Paine, J. R., and Wangenstein, O. H.: Pressure in Experimental and Clinical Intestinal Obstruction, *Proc. Soc. Exper. Biol. & Med.* 32:1504-1506, 1935. We once observed rupture of a distended loop of bowel on its escape from the abdomen. We found by experiment that a piece of fresh human ileum ruptured at a pressure of 210 mm. of mercury.

pressure. Flaccidity and blueness of a distended bowel show that at one time there was a high pressure within it.

We do not deny that the bowel is somewhat injured by a prolonged pressure as low as 22 mm. of mercury or that prolonged inflation of long stretches of the small bowel at this level of pressure will cause death, but we do deny that this pressure acting continuously for twelve hours or more will cause any significant change in the vitality or the structure of the bowel. Analysis of Sperling's experiments supports this conclusion. We have demonstrated this by a number of experiments. The clinical and the experimental evidence both support the conclusion that acute and serious injury to the bowel by intrainestinal pressure occurs only when this pressure is near the diastolic blood pressure and persists for several hours.

The foregoing considerations guided us in planning our experiments.

PROTOCOLS OF EXPERIMENTS

SERIES 1 (8 dogs).—Experiments Designed to Show the General Effects of Distention on the Bowel.—Sodium amytal was given intravenously to induce anesthesia. A piece of the small intestine was delivered through a short incision, gently stretched and divided into three segments of equal length (20 cm. each), careful allowance being made for the small lengths of bowel necessary for ligation. One segment was excised and weighed. The remaining segments were inflated with pressures ranging from 22 to 74 mm. of mercury in different experiments. Pressure was maintained for four hours, then released in one segment but maintained in the other for thirty minutes more. Then both segments were excised and weighed.

Results.—Segments in which pressure was maintained throughout the experiment decreased on the average about 2 Gm. in weight. Segments in which the pressure was released during the final thirty minutes of the experiment showed an increase of approximately 20 per cent of their original weight. Segments in which the pressure was maintained throughout the experiment remained dry and pale; segments in which pressure was released thirty minutes before the close of the experiment became dusky and edematous.

Practically no fluid was found in the lumens of any of the loops. Drops of fluid were seen over the surfaces of all distended loops. Analysis of this fluid showed that it contained: total protein, 3.7 per cent; albumin, 3.2 per cent; globulin, 0.5 per cent.

Sections for microscopic study of the segments kept inflated throughout the experiments showed compression of the tissues, especially of the mucosa, and absence of blood in the capillaries and the veins. Sections of segments deflated thirty minutes before the close of the experiments showed edema of the mucosa, slight loss of epithelium or no loss at all, slight extravasation of blood, considerable accumulation of blood in the capillaries and veins and great edema of the fat at the mesenteric border of the bowel.

Conclusions.—Our conclusions from this series of experiments are: (1) that an intrainestinal pressure of 22 mm. of mercury or more maintained for several hours decreases the quantity of fluid in the

wall of the bowel and that, up to a certain limit, the greater the pressure, the greater the decrease of fluid; (2) that part of this loss of fluid is due to a sweating of albuminous fluid from the peritoneal surface of the bowel, and (3) that a piece of bowel which has been kept distended for several hours increases in weight and becomes markedly edematous and cyanotic after the distention is released.

SERIES 2 (4 dogs).—Experiments to Determine the Cause of the Increase in Weight of the Bowel Following the Release of Pressure.—In this series we repeated the experiments just described except that we injected 20 cc. of a 1 per cent solution of trypan blue into the femoral vein thirty minutes before the close of the experiments, at the time the pressure was released from one of the segments.

Results.—Within two or three minutes after the injection of the dye, the deflated segments of the bowel started to turn blue, and this color darkened progressively until the end of the experiment. Segments which were kept inflated and the untreated intestines showed no change in color.

We had to consider that the trypan blue in the damaged bowel might be entirely in the capillaries and not in the tissue spaces. It is impossible to demonstrate microscopically the extravasation of trypan blue into the tissue, for during the process of fixation the dye diffuses out. We obtained conclusive proof of abnormal capillary permeability by observing a blue stain on blotting paper held against the bowel.

In some experiments a suspension of india ink was used instead of trypan blue. Microscopic study of the bowel in the experiments in which the india ink was used revealed the presence of edema in all coats of the bowel and in the mesenteric fat. The epithelium of the mucosa showed little or no change from normal. There were small hemorrhages in the submucous coat. The blood vessels were dilated and in some instances outlined by india ink adherent to their walls. In other areas the blood vessels contained clumps of india ink. In all parts of the sections studied particles of india ink could be identified in the tissues, especially in the mesenteric fat, and in the submucous and muscular coats of the bowel.

Conclusions.—Distention of the bowel by pressures which impede the circulation in the wall to a considerable degree for several hours damages the capillaries so that they become permeable to the blood proteins. This leads to an escape of blood proteins into the tissues of the bowel after the release of pressure. Therefore a part of the increase in weight of the bowel after the release of distention is due to edema caused by the escape of plasma from capillaries. The other part must be due to the excessive quantity of blood in the capillaries.⁴

Why does blood accumulate in the capillaries of a bowel in the second stage of distention? We once held the common opinion that distention of the bowel causes obstruction to the venous outflow of the bowel. We suggested that the accumulation of blood might be due to

4. Sperling, L.: Mechanics of Simple Intestinal Obstruction: An Experimental Study, Arch. Surg. 36:778-815 (May) 1938.

torsion of the mesenteric veins and to pressure on them by distended loops of the bowel.⁵ Direct observation of the effects of distention of the bowel on the mesentery convinced us that this explanation is not true. We therefore looked for another.

It occurred to us that the cause of the congestion observed in the second stage of distention of the bowel might be vasomotor paralysis of the arterioles in the wall of the bowel. We have been unable to find any report on this effect of distention. We made the following observations a number of times in the course of experiments for other purposes: (1) When a segment of the bowel is kept tense for several minutes by inflation and then suddenly deflated, it suddenly assumes a bright red color which contrasts sharply with the paler hue of the bowel on each side of it. The bright color fades in a few minutes. This effect is the same as that observed on the skin of the forearm after the release of a tourniquet placed around the arm. (2) When the bowel is kept tense for several hours and then deflated, it becomes and remains cyanotic. The first effect is due to a temporary vasomotor paralysis; the second, to a more lasting one.

SERIES 3 (10 dogs).—Experiments to Determine the Quantity and the Composition of the Fluid Found in the Peritoneal Cavity as a Result of Distention of the Bowel.—Control Experiment: Sodium amytal was given intravenously to a dog to induce anesthesia. Laparotomy was then performed. The pylorus was ligated. The terminal part of the ileum was divided and a tube inserted into the proximal end. The tube was brought out through the abdominal incision which was then closed. The experiment occupied four hours. No fluid could be collected from the peritoneal cavity.

Experiments: Various experiments were performed in which the procedures outlined for the control experiment were carried out and in which in addition the bowel was inflated with pressures ranging in different experiments from 22 to 100 mm. of mercury. In each experiment only one pressure was used, and this was maintained constantly for six hours.

Results.—The results of these experiments are shown in detail in table 1.

Conclusions.—The quantity of fluid in the peritoneal cavity as a result of distention of the bowel tends to increase as the pressure in the bowel increases. It also tends to increase with the duration of the distention (see data on dogs 2 and 10 in table 1). Analysis shows that this fluid contains approximately half as much protein as the blood plasma and relatively more than half as much albumin. In protein content the fluid is equal to about half its volume of plasma. Dog 8, for example, lost about one fifth of its total quantity of blood protein in the peritoneal fluid.

5. Gatch, W. D., and Culbertson, C. G.: Circulatory Disturbances Caused by Intestinal Obstruction, *Ann. Surg.* **102**:619-635, 1935.

A considerable quantity of intraperitoneal fluid is always found in human patients with obstruction of the bowel. Recently, in a patient with obstruction due to a gallstone impacted in the lower part of the ileum, we found a large quantity of this fluid; analysis showed the following composition: total protein, 4.2 per cent; albumin, 3.4 per cent; globulin, 0.8 per cent. These percentages are a little higher than those for the fluid obtained from experimental animals.

TABLE 1.—*Data on Experiments to Determine the Quantity and the Composition of the Fluid Found in the Peritoneal Cavity as a Result of Bowel Distention*

Dog	Weight of Dog, Kg.	Intra-intestinal Pressure, Mm. of Mercury	Duration of Experiment, Hr.	Amount of Fluid Collected, Cc.	Analysis of Fluid		
					Total Protein, per Cent	Albumin, per Cent	Globulin, per Cent
1	12.9	22.0	6	50			
2	12.1	29.0	6	100			
3	10.0	29.6	6	125	4.5	2.9	1.6
4	14.0	33.0	6	85			
5	13.0	44.0	6	150	3.0	2.3	0.7*
6	13.0	59.0	6	150	2.8	2.2	0.6
7	12.5	62.0	6	155	3.6	2.7	0.9
8	13.0	74.0	6	200			
9	10.0	100.0	6	250			
10	15.0	29.0	16	195			

* Analysis of the blood plasma of this dog showed: total protein 7.1 per cent; albumin, 4.2 per cent; globulin, 2.9 per cent.

TABLE 2.—*Data on Experiments to Determine the Origin of the Fluid Found in the Peritoneal Cavity in the Presence of Distention of the Bowel*

Dog	Experiment	Weight of Dog, Kg.	Length of Bowel Segments, Gm.	Weight of Segment A, Gm.	Weight of Segment B at the Close of the Experiment, Gm.	Increase in the Weight of the Gauze, Gm.	Pressure, Mm. of Mercury	Hematocrit Determinations, per Cent		Time, Hr.
								Initial	Final	
1	1	13.8	30.0	22.0	21.9	5.0	59	48	54	3
2	2	5.7	16.5	20.5	20.5	4.0	22	3
2	3	...	16.5	20.5	17.1	6.1	44	3
2	4	...	16.5	20.5	19.0	10.0	74	3

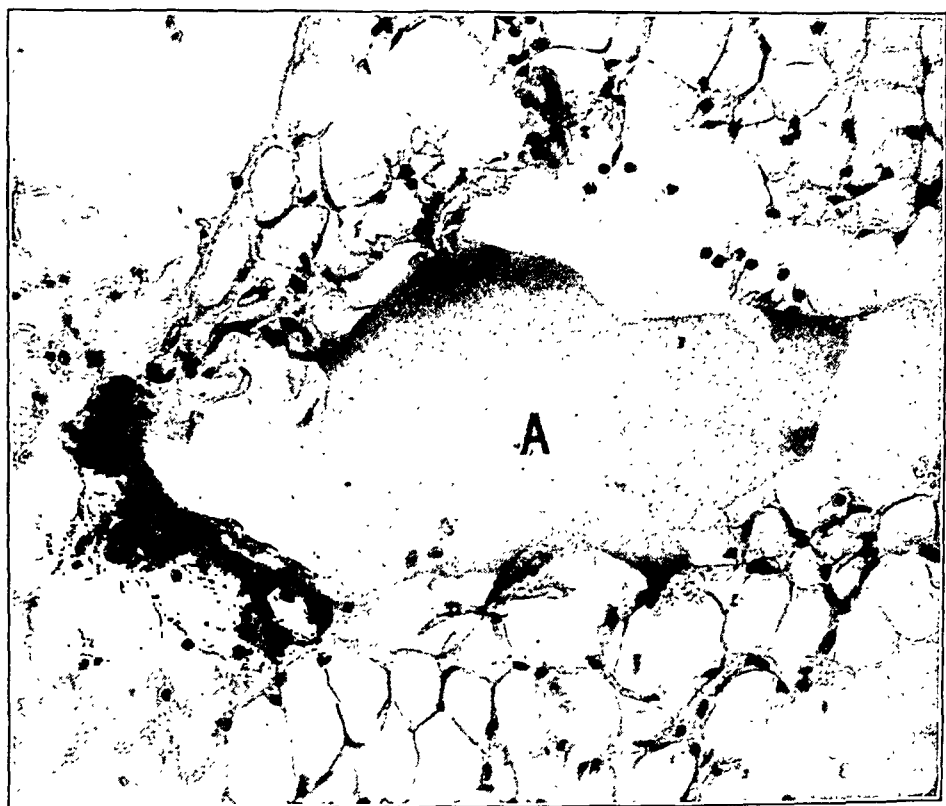
SERIES 4 (2 dogs).—*Experiments to Determine the Origin of the Fluid Found in the Peritoneal Cavity in the Presence of Distention of the Bowel.*—Anesthesia was induced with sodium amytal and laparotomy performed. Two contiguous segments of bowel of equal length were used for each experiment. One segment (A) was excised and weighed; the other (B) was kept inflated to a constant level of pressure, having first been wrapped in dry weighed gauze. At the end of the experiment the gauze and segment B were each weighed.

Results.—The results of these experiments are given in table 2. Analysis of the fluid wrung from the gauze used in experiments 2 and 3 showed: total protein, 3.7 per cent; albumin, 3.2 per cent; globulin, 0.5 per cent.

Conclusions.—Our conclusions from this series of experiments are: (1) that the peritoneal fluid comes in part from the distended bowel;

(2) that the quantity of the fluid increases as the intrainestinal pressure increases (experiments 2, 3 and 4 were all done on the same dog); (3) that constant distention causes a slight loss in the weight of the bowel but this loss is far less than the weight of the fluid absorbed by the gauze.

Whence came the greater part of this fluid? Our answer is that it came from the tissue along the mesenteric border of the bowel. In all the foregoing experiments a constant finding was a great edema of this tissue; this is illustrated in the photomicrograph. In many experi-



Photomicrograph of the fat at the mesenteric border of a bowel which had been kept tightly distended for some time. *A*, edematous fluid.

ments the mesenteric border of the bowel was $\frac{1}{2}$ inch (1.2 cm.) thick, and fluid dripped from it when it was cut. In experiment 2 of series 4 the pressure used was 77 mm. of mercury. The weight of the gauze increased 10 Gm., and that of the bowel decreased 1.5 Gm. Therefore, 8.5 Gm. of the fluid absorbed by the gauze must have come from the mesenteric fat, since there was no other source for it. With a lower intrainestinal pressure it is probable that the part of the fluid derived from the bowel would be relatively greater.

There is, we believe, a complete and satisfactory explanation for the edema of the fat at the mesenteric border of the bowel.

Gatch, Trusler and Ayers^{1a} observed that there is always some flow of blood, which no degree of intrainstestinal pressure will stop, from the vein which drains a distended loop of bowel. They attributed this to small anastomotic arteries at the mesenteric border. Dragstedt^{1b} concurred in this explanation and recorded the observation that with maintenance of distention the flow in question gradually increases until it equals the flow through the unobstructed bowel. This explains the maintenance of the flow of blood through the mesentery when circulation through the intestine is arrested by distention. It accounts also for the exudation of fluid from the capillaries at the mesenteric border in the presence of bowel distention, because then these capillaries must dilate to make room for a much greater volume of blood than that to which they are accustomed.

SERIES 5.—*Experiments to Determine Whether After the Release of Prolonged Distention There Is a Loss of Blood Proteins into the Tissues and Mesentery of the Bowel and into the Peritoneal Cavity Sudden Enough and Great Enough to Cause Concentration of the Blood.*⁶—Experiment 1: The entire small intestine of a dog was kept inflated with a pressure of 44 mm. of mercury for four and a half hours.

The hematocrit reading at the start of the experiment was 49 per cent; after four and a half hours of inflation it was 55 per cent; fifteen minutes after deflation it was 57 per cent; thirty minutes after deflation it was 59 per cent.

Experiment 2: The entire small intestine of a dog was kept inflated with a pressure of 71 mm. of mercury for four hours. The hematocrit reading at the start of the experiment was 41 per cent; after four hours of inflation it was 60 per cent; thirty minutes after deflation it was 63 per cent.

Experiment 3: The entire small intestine of a dog was kept inflated with a pressure of 61 mm. of mercury for six hours. The hematocrit reading at the start of the experiment was 42 per cent; after six hours of inflation it was 66 per cent; fifteen minutes after deflation it was 68 per cent.

Experiment 4: The entire small intestine of a dog was kept inflated with a pressure of 71 mm. of mercury for four hours. The hematocrit reading at the start of the experiment was 41 per cent; after four hours of inflation it was 60 per cent; thirty minutes after deflation it was 63 per cent; at intervals of thirty minutes for a period of two hours it remained 59 per cent.

Experiment 5: The entire small intestine of a dog was kept inflated with a pressure of 50 mm. of mercury for four hours. The hematocrit reading at the start of the experiment was 45 per cent; after four hours of inflation it was 61 per cent; then for five determinations made at intervals of thirty minutes it remained 63 per cent.

Conclusions.—The results indicate that after deflation of a small bowel which has been tightly distended for four hours there is a slight

6. Elman, R.: The Danger of Sudden Deflation of Acute Distended Bowel in Late Low Intestinal Obstruction, *Am. J. Surg.* **26**:438-446, 1934. Ochsner, A., and Storck, A. H.: Mechanical Decompression of the Small Intestine in Ileus, *J. A. M. A.* **108**:260-266 (Jan. 23) 1937. Fine, J.; Fuchs, F., and Gendel, S.: Changes in Plasma Volume Due to Decompression of the Distended Bowel, *Arch. Surg.* **40**:710-716 (April) 1940.

increase in the concentration of the blood. It seems certain that this concentration is due to the escape of blood plasma into the tissue spaces of the deflated bowel. We had the idea that this concentration might be great enough and sudden enough to explain death which sometimes follows shortly after deflation of a distended bowel in man, but the increases in the blood concentration which we observed in these experiments were too small to lend much support to this hypothesis. It next occurred to us that in addition to this loss of plasma the circulation would lose a considerable quantity of whole blood pooled in the capillaries of the deflated bowel. With this thought in mind we repeated the foregoing experiments on 2 dogs and measured the blood volume before and after deflation. The loss in blood volume was so small that it came within the experimental error of the method. It is well known, however, that the determination of the blood volume in the presence of hemoconcentration or of an impairment of circulation due to other causes is inaccurate. Simple inspection shows that the deflated bowel contains an abnormal amount of poorly oxygenated blood. The experiments in series 1 showed that the bowel on deflation after four to six hours of tight inflation increases in weight by about 20 per cent. The small intestine of a dog is about 320 cm. in length. We determined by many estimations that its weight on the average is about 1 Gm. per centimeter. An increase of one fifth of this weight would require 75 to 100 cc. of blood and plasma. We believe that this is an accurate estimate of the loss of blood and plasma from the circulation following deflation. When the circulation of an animal is in a precarious condition owing to hemorrhage or hemoconcentration, it is well known that a comparatively small loss of blood is fatal. Therefore, we think it reasonable to believe that death following shortly after the sudden deflation of long pieces of a distended bowel may in some cases be explained by the pooling of blood in the deflated bowel.

The foregoing remarks apply to the effects of deflating a bowel in the first stage of distention. The deflation of a bowel in the second stage of distention by the operation of stripping might be fatal by reason of hemorrhage into the wall of the lumen of the bowel. The tissues of a bowel in the second stage of distention are extremely weak and bleed freely.

SUMMARY AND CONCLUSIONS

Injury to the bowel by distention depends not only on the distending pressure but also on the diastolic blood pressure. Pressures less than half the diastolic blood pressure do but little injury to the bowel unless they act continuously for a long time.

Distention great enough to injure the bowel tends to pass through two stages which are clearly defined in both human beings and experimental animals. The bowel is tense and anemic in the first stage and

flaccid and congested in the second. It passes from the first to the second stage when its wall stretches enough to permit resumption of flow of the blood in fair volume through its capillaries. It is being injured in the first stage; it is recovering from this injury in the second. Failure to recognize the occurrence of these two stages has led to much error in the interpretation of results of experiments on distention.

Most of the albuminous fluid found in the peritoneal cavity in the presence of bowel obstruction accumulates there in the first stage of distention. Some of it is squeezed out of the bowel wall, but the greater part escapes from the fat along the mesenteric border of the bowel.

The quantity of this fluid varies with the duration of the first stage of distention and with the degree of obstruction to the flow of blood in the wall of the bowel attendant on distention.

The protein content of the peritoneal fluid is about half that of plasma and consists chiefly of albumin. Damage to the capillaries by distention is evidently not so serious as that due to burns or inflammation which makes the capillary endothelium incapable of holding back the large globulin molecules.

No fluid accumulates in the lumen of the bowel in the first stage of distention; our experiments do not show whether it accumulates in the second stage.

The cyanosis of the bowel in the second stage of distention is due to vasomotor paralysis and to the relaxation of the tissues which support the capillaries. It is not due to venous obstruction.

CLINICAL APPLICATIONS

The quantity of albuminous fluid lost to the circulation because of the effects of distention on the bowel is probably of no great importance except in cases of rapidly developing and great distention. When the distention develops slowly, the body can probably produce blood protein as rapidly as it is lost. Our clinical observation supports this idea.

In cases of intestinal obstruction in man both stages of distention may be present. The part of the bowel immediately above an obstruction which has been present for some time may be in the second stage of distention; the part of the bowel above this may be in the first stage. At a still higher level the bowel may be found dilated, although it may not be dilated enough to prevent it from contracting. Pressure is not the same in all parts of the intestine.

Death occurring shortly after the rapid deflation of a distended bowel may be due in some cases to a sudden loss of blood and plasma from the circulation.

Our observations seem to indicate that the best treatment of intestinal obstruction is intestinal intubation, followed by enterostomy if at operation the bowel is found in a badly damaged condition. A bowel

in the second stage of distention cannot contract or perform any of its functions in a normal way. Therefore, actual removal of the cause of obstruction may not relieve the obstruction until a long time afterward.

Our experiments were confined to the effects of distention on the small bowel, but we believe that with certain reservations the conclusions apply to the large bowel as well. In man the large bowel can be tremendously dilated without much interference with its circulation, but once the pressure within it approaches the diastolic blood pressure, the large bowel will, there is every reason to believe, suffer the same damage as the small bowel. Surgeons do not often observe this damage to the large bowel because of the latter's distensibility and because as a rule distention increases slowly and is relieved by colostomy before it does serious harm. However, most surgeons have observed at operation or autopsy rupture of the large bowel caused by distention.

RIB RESECTION IN THE TREATMENT OF SCOLIOSIS

H. LESLIE WENGER, M.D.

NEW YORK

Although there have been some satisfactory results obtained by the use of the more recently developed method of treatment for scoliosis (particularly by the turnbuckle jacket with eventual fusion of the primary curve), these procedures still leave much to be desired. Because of the small percentage of really good results, the prolonged period of hospitalization and the consequent high cost of the treatment, a more satisfactory method would indeed be welcome.

The treatment of scoliosis by rib resection was originally suggested to Hoffa¹ by Volkmann² in 1889. In this country in 1902, Hoke³ performed rib resection on a 16 year old girl with a high right dorsal curve (the apex was at the level of the eighth thoracic vertebra). He had tried postural treatment and braces unsuccessfully before operating. The prominence of the ribs extended from the fourth rib down on the right side. After trying rib resection on a cadaver, he operated on the patient. This was done in three stages.

The first stage consisted of resection of the fifth to the eighth ribs inclusive, on the left side. Hoke justified his procedure by saying that:

. . . as long as that area was sunken in, the plane of the chest wall would be such that the left shoulder must glide backwards towards the spine; and because the position of these ribs and their attachment to the spine opposed structurally the counter-rotation efforts.

Six weeks later he performed osteotomy of the ribs on the right side and resected five ribs. Four months later the third operation was done.

No roentgenograms were made at that time, but the published photographs look good.

The procedure was certainly considered radical and was likely associated with a great deal of shock to the patient. The first stage took three and a half hours to perform.

1. Hoffa, A.: Operative Behandlung einer schweren Skoliose (Resection des Rippenbuckels), *Ztschr. f. orthop. Chir.* 4:402-408, 1895-1896.

2. Volkmann, R.: Rippenresection bei der Skoliose, *Berl. klin. Wchnschr.* 26:1097, 1889.

3. Hoke, M.: A Study of a Case of Lateral Curvature of the Spine: A Report on an Operation for the Deformity, *Am. J. Orthop. Surg.* 1:168-208, 1903-1904.

In more recent years, when rib resection had become a common procedure in the treatment of tuberculosis, it was immediately noted that in many of the patients some curvature of the spine developed as a result of thoracoplasty.

In 1934, Bisgard,⁴ working in the field of thoracic surgery, reported a series of cases and pointed out some important facts. He was chiefly concerned with preventing scoliosis after rib resection, and he stated

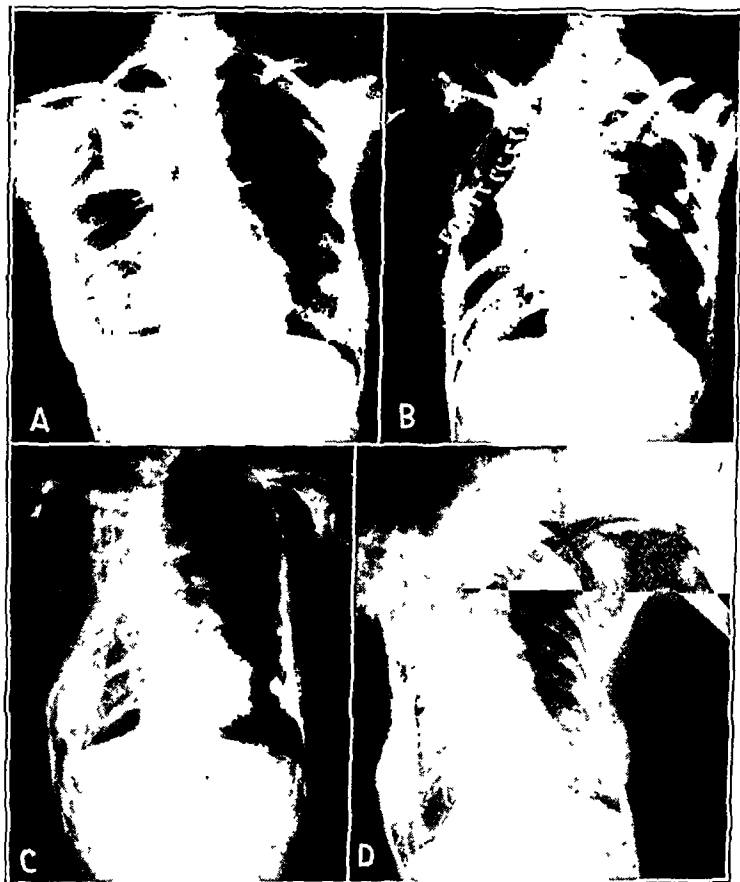


Fig. 1.—Roentgenograms of G. B.: *A*, taken before operation, shows extensive tuberculosis with cavitation in the right side of the thorax. *B*, taken in September 1936, after a two stage thoracoplasty by which six ribs were removed, shows the transverse process of the second thoracic vertebra destroyed and large stumps where the other ribs were removed. *C*, taken seven months after thoracoplasty, shows curvature of the spinal column with the deforming convexity localized at the third thoracic vertebra. *D*, taken in June 1940, after two more ribs were resected, revision performed and more transverse processes removed, reveals that the curve of the spinal column has been aggravated.

4. Bisgard, J. D.: Thoracogenic Scoliosis: Influence of Thoracic Disease and Thoracic Operations on Spine, *Arch. Surg.* 29:417-445 (Sept.) 1934.

some conclusions which must be considered as extremely important to the orthopedic surgeon.

His principal observations were that a convexity occurred toward the side on which the operation was performed and that this convexity depended on three factors: (1) the number and the length of the dorsal segments resected; (2) the site of the rib resection, because the higher the area of the operation, the greater the effect on the



Fig. 2.—Roentgenograms of E. B.: *A*, taken in January 1938, shortly before operation, discloses marked tuberculosis in the right side of the thorax but no deviation of the spinal column. *B*, taken after extensive thoracoplasty, shows the transverse processes intact and no deviation of the spinal column. *C*, taken a few months later, demonstrates that scoliosis is still absent in spite of the operation.

curvature, and (3) the relative position of the resected rib to the spine, because the greater the proximity, the greater the effect on the curvature.

The thoracic explanations which Bissard offered to clarify the phenomena were not entirely correct and were somewhat confusing. However, much credit must be given to him for his general observations,

because these made orthopedic surgeons look with interest on the possibility of using the procedure in the treatment of scoliosis.

The present study was made with these facts in mind. All the available material at Sea View Hospital was reviewed. There were some insurmountable obstacles. Roentgenograms are kept for only five years unless the patient is still being treated at the end of that time. In many cases the roentgenograms were not taken with a Bucky diaphragm, and the spine showed up so poorly that the material was unsatisfactory for analysis. However, in spite of these handicaps, it was possible to collect 256 cases in which rib resection had been performed. Cases in which the extensive Shede operation had been performed were intentionally omitted, as this operation is not applicable to the treatment of scoliosis

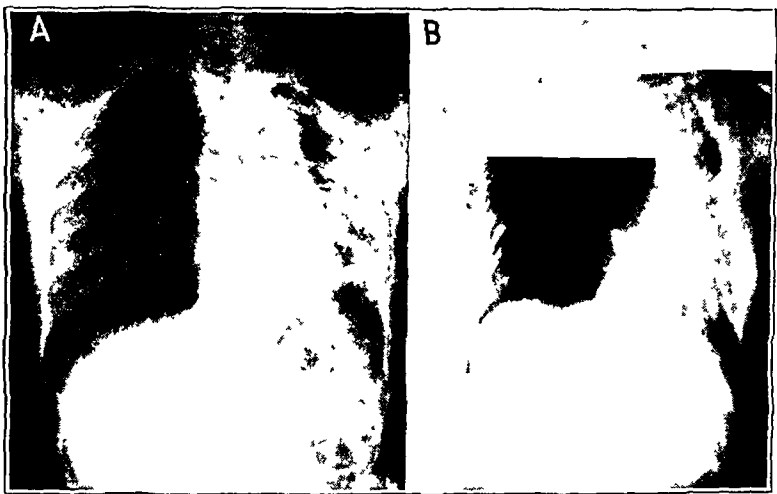


Fig. 3.—Roentgenograms of G. C. (the case of this patient was reported some years ago by Dr. M. Cleveland): *A*, taken after an unsuccessful attempt at artificial pneumothorax, shows extensive tuberculosis in the left side of the thorax; *B* was made after extensive resection by which eleven ribs were removed; the only transverse processes left intact are those of the first, second and third thoracic vertebrae; marked scoliosis is present.

Every effort was made to limit the study to those patients who underwent only rib resection.

A survey of all the roentgenograms of patients on whom thoracoplasty had been done was made with the idea of determining the cause of the characteristic scoliosis in these patients. The study was undertaken for the purpose of possibly using the essential parts of the operation to treat primary scoliosis.

The total number of cases in which resection was performed was 256; 140 of the patients were men, 107 were women, and 9 were children. Before operation 30 of the patients had scoliosis. Postoperative scoliosis

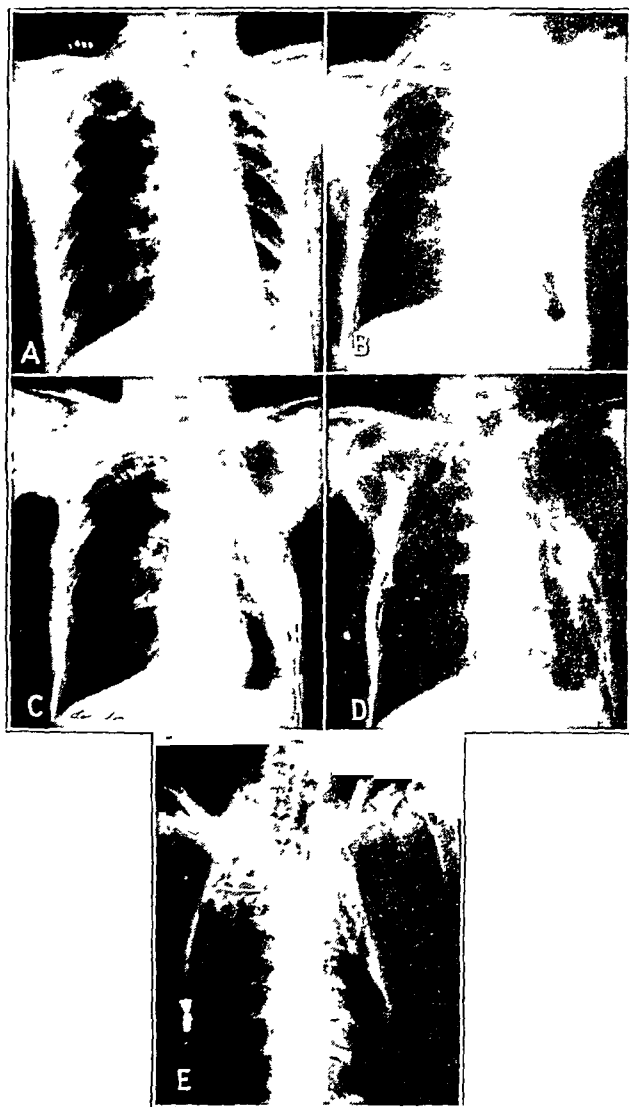


Fig. 4.—Roentgenograms of L. D.: *A*, taken before operation, reveals far advanced tuberculosis with excavation in the upper portions of the fields of both lungs; the spine is straight. *B*, made after a two stage thoracoplasty by which the upper seven ribs were removed from the left side, shows the transverse processes intact and short sections of the ribs remaining. *C*, taken after a one stage thoracoplasty by which the upper three ribs were removed from the right side, shows the transverse processes left intact. *D*, taken after a second stage thoracoplasty by which two more of the upper ribs were removed from the right side, shows the transverse processes intact and no scoliosis. *E*, made after a third stage thoracoplasty by which one more rib was removed from the right side (this made a total of seven ribs removed from the left and six from the right side), shows all transverse processes intact and the spinal column still straight.

with a shift of the deforming convexity to the side opposite that on which resection had been done or with overcorrection affected 11 men and 9 women. The relation of scoliosis to the type of operation and the number of ribs resected is shown in the table. In the 140 cases in which the patients were men, there was a shift of the spinal column to the right after rib resection in 55, a shift to the left in 67 and no shift at all in 18. In the 107 cases in which the patients were women there was a shift of the spinal column to the right after rib resection in 48, a shift to the left in 40 and no shift at all in 19."

It has been pointed out on numerous occasions that scoliosis after intrathoracic pathologic change is of two main types. In the first type



Fig. 5.—Roentgenograms of M. S. H.: *A*, taken on admission, shows evidence of a basal thoracoplasty performed elsewhere and practically no deviation of the spinal column. *B*, taken after more extensive thoracoplasty, shows the transverse processes intact and only a little deviation of the spinal column.

Relation of Scoliosis to the Stage of Resection and the Number of Ribs Resected

Stage of Resection	Ribs Resected in Men with Scoliosis		Ribs Resected in Men Without Scoliosis		Ribs Resected in Women with Scoliosis		Ribs Resected in Women Without Scoliosis	
	Right	Left	Right	Left	Right	Left	Right	Left
First.....	7	6	5	6	5	4	5	6
Second.....	19	32	3	4	18	20	4	0
Third.....	29	29	0	0	25	16	2	2
Total.....	55	67	8	10	48	40	11	8

there is concavity to the diseased side, such as occurs with pleural or pulmonary diseases in which the chronic inflammatory processes result in extensive scar tissue contraction. The second type is scoliosis after

thoracoplasty. In the latter there is always convexity to the side on which operation has been performed.

One readily understands, then, that a patient with a chronic disease of the lungs has a scoliotic deformity to one side and that after thoracoplasty the spine shifts with the convexity to the opposite side. The questions naturally arise: What element causes this shift? Can this

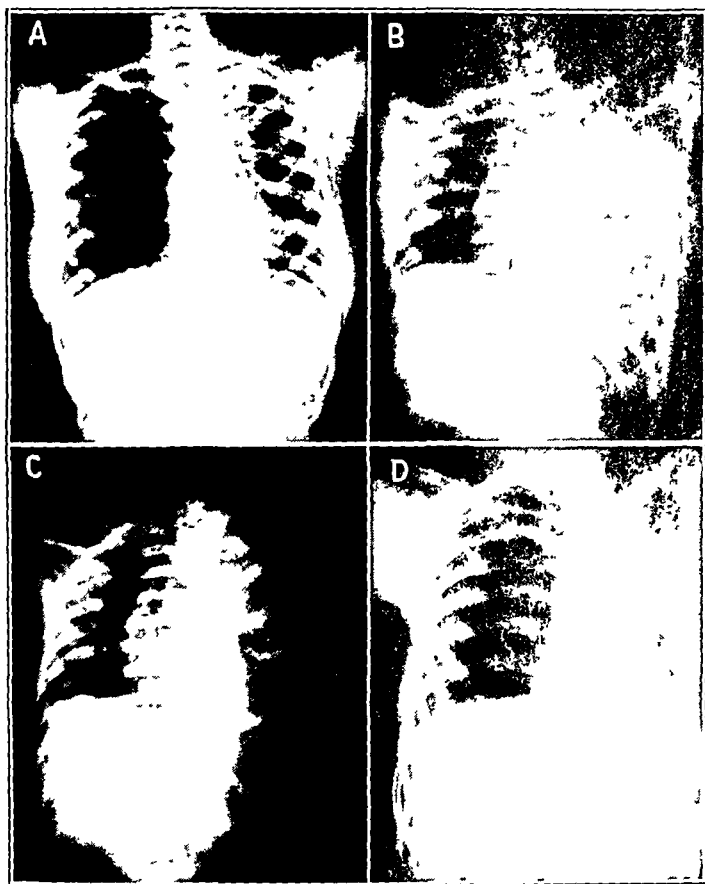


Fig. 6.—Roentgenograms of E. L.: *A*, made in February 1933, shows far advanced caseous pneumonic disease with a large excavation in the upper two thirds of the field of the left lung; there is a slight, gentle C curve in the spinal column, which is probably a postural condition. *B*, taken in 1933, after a one stage thoracoplasty by which the upper four ribs were removed, demonstrates that the transverse processes of the third and fourth thoracic vertebrae have been partially destroyed and that there is little change in the contour of the spinal column. *C*, taken six months later, after a more complete thoracoplasty by which the upper ten ribs were removed, shows that the transverse processes from the third to the tenth thoracic vertebrae have either been destroyed or removed and that there is a C curve in the spinal column with its apex at the level of the fifth thoracic vertebra which shows greater curvature than the original postural defect. *D*, taken four months later, shows little change in the curvature of the spinal column and considerable regeneration of the ribs along the spinal column.

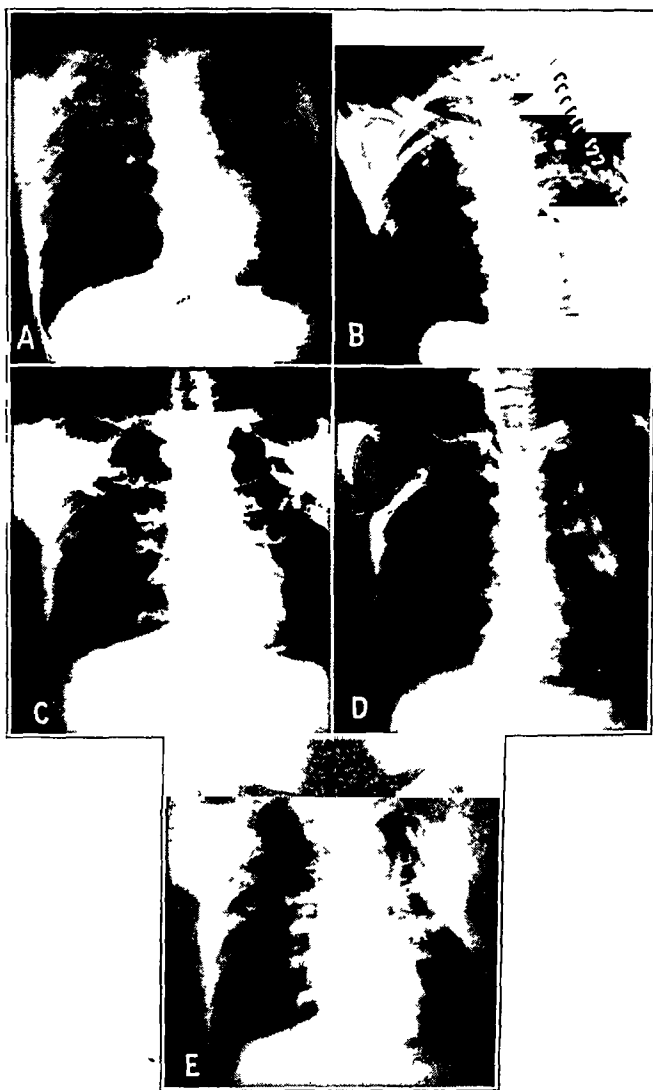


Fig. 7.—Roentgenograms of I. S.: *A*, taken in June 1936, shows far advanced caseous pneumonic disease with numerous cavities in the upper half of the fields of both lungs and the spinal column straight. *B*, taken in November 1936, after a one stage thoracoplasty by which the upper four ribs were removed from the left side, shows the transverse processes intact. *C*, made on June 3, 1937, after a one stage thoracoplasty by which four ribs were removed from the right side, shows the transverse processes intact and the spinal column straight. *D*, made on June 23, 1937, after a second stage thoracoplasty by which three more ribs were removed from the left side, shows the transverse processes intact, large segments of the ribs visible and the spinal column straight. *E*, made in March 1940, after a bilateral thoracoplasty by which seven ribs were removed from the left side and four from the right, shows the transverse processes intact and the spinal column straight.

element be determined in advance? How many ribs must be resected and where must this resection take place?

Analysis shows the following facts:

1. In the majority of the cases there was convexity of the spine toward the operative side.

2. The number and the length of the costal segments resected do not of themselves alter the resulting scoliosis.

3. In all cases in which there was marked convexity to the side on which operation had been performed either the transverse process was injured or the anterior costotransverse ligament was cut. In cases in which the transverse processes were left intact, slight curvature or none at all resulted.

4. In all the cases (3.5 per cent) in which the patients were children there was destruction of the transverse processes. This possibility explains the severe postoperative curvature.

5. Resecting a larger number of ribs does not necessarily increase the curvature. However, if a transverse process is injured or removed the curvature occurs.

6. Resection lateral to the angles of the ribs causes practically no deviation except in children.

7. There are no sharply angulated curves; that is, there are no wedged vertebrae. (All are C curves.)

8. As successive rib resections are carried out at lower levels, the apex of the curve descends.

9. Mediastinal displacement does not necessarily cause scoliosis.

10. There was no change in spinal curvature in 7 cases in which basal thoracoplasty was performed. Apparently basal thoracoplasty has little effect on the spine.

11. In cases in which successive ribs are removed and at one point a transverse process is resected, the apex of curve suddenly localizes at that point, and the curve increases.

12. Regeneration of ribs will prevent scoliosis.

13. In all cases the resulting curve averaged 18 degrees.

To the orthopedic surgeon the foregoing analysis is especially significant. The question naturally occurs: Can a similar procedure be carried out in order to correct preexisting true scoliosis? There is evidence that this use of the procedure is worth investigating; in fact, it has already been attempted. These studies favor strongly the opinion that the essential element is not the rib but the transverse process.

An attempt at explanation of the observed phenomena is intentionally avoided. The pathologic physiology of this condition has as

yet not been adequately expounded. Such explanations as have been given are hypothetical.

CONCLUSION

The main conclusions of this study are that scoliosis resulting from thoracoplasty is due to trauma or removal of the transverse processes and that the rib resection of itself has little if any influence in causing the condition. On the basis of these findings transversectomy to correct primary scoliosis is now being done on the concave side of the spinal curvature.

CAPILLARY PERMEABILITY AND INFLAMMATION IN RABBITS WITH STAPHYLOCOCCIC SEPTICEMIA

AN EXPERIMENTAL STUDY

R. H. RIGDON, M.D.

MEMPHIS, TENN.

Capillary permeability and inflammation have been studied recently in the rabbit under varying experimental conditions. Observations on the localization and the concentration of intravenously injected trypan blue in the skin of the normal animal have shown that this dye localizes and concentrates only during a specific interval following the local application of xylene.¹ This interval is not determined by either the presence or the absence of edema and hyperemia. Furthermore, the time in which the greatest number of leukocytes localize in the xylene-treated areas of the skin follows by several hours the localization and the concentration of the dye.^{1b}

Materials such as vaccine virus, india ink, antitoxin and staphylococci when given intravenously localize and concentrate in areas of inflammation in a manner similar to that of trypan blue.² Both capillary permeability and the localization of leukocytes in areas of injury are affected by alcohol, by certain anesthetics and by epinephrine.³ Pickrell^{3a} found that alcoholic intoxication maintained at the point of stupor destroys the resistance of the rabbit to pneumococcal infection. According to Pickrell, this loss of resistance "appears to be due to the fact that intoxication profoundly inhibits the vascular inflammatory response as long as

From the Department of Pathology, University of Tennessee College of Medicine.

This study was aided by grants from the John and Mary R. Markle Foundation and from the University of Tennessee.

1. Rigdon, R. H.: (a) Capillary Permeability in Areas of Inflammation Produced by Xylene, *Arch. Surg.* **41**:101 (July) 1940; (b) Relation of Capillary Permeability to Inflammation, *South. M. J.* **34**:292, 1941.

2. Rigdon, R. H.: Localization of Staphylococcus Antitoxin in Areas of Inflammation, *J. Lab. & Clin. Med.*, to be published; footnote 1.

3. (a) Pickrell, K. L.: The Effect of Alcoholic Intoxication and Ether Anesthesia on Resistance to Pneumococcal Infection, *Bull. Johns Hopkins Hosp.* **63**:238, 1938. (b) Cressman, R. D., and Rigdon, R. H.: Capillary Permeability and Inflammation in Narcotized Rabbits, *Arch. Surg.* **39**:586 (Oct.) 1939. (c) Rigdon, R. H.: A Study of Capillary Permeability and Inflammation in the Skin of Rabbits Given Adrenalin, *Surgery* **8**:839, 1940.

the intoxication is maintained . . ." Leukocytes fail to emigrate to the bacteria. Cressman and Rigdon^{3b} observed that "capillary permeability in areas of inflammation is altered in rabbits narcotized with alcohol or ether, as demonstrated by the localization and concentration of trypan blue."

Epinephrine given either intradermally or intravenously in large quantities inhibits the development of hyperemia in the areas of the skin to which xylene has been applied. The number of polymorphonuclear leukocytes is decreased around staphylococci when epinephrine is injected intradermally. "The failure of leucocytes to reach an area infiltrated with staphylococci when the animal is given large quantities of adrenalin either intradermally or intravenously apparently may be the result of vascular constriction."^{3c}

In a group of rabbits given staphylococci intravenously polymorphonuclear leukocytes failed to localize in the xylene-treated areas of the skin.⁴ This observation appears significant, since the absence of leukocytes may be due either to a diminution in the number of white blood cells in the circulating blood or to some local vascular or tissue change. This paper presents a further study of capillary permeability and inflammation in the skin of rabbits with staphylococcic septicemia.

CAPILLARY PERMEABILITY IN THE SKIN OF RABBITS AFTER THE INTRAVENOUS INJECTION OF STAPHYLOCOCCI

The technic used in this experiment for the study of capillary permeability is the same as that used in earlier investigations.⁵ The skin over the sides and the abdomen of the rabbit is carefully shaved twenty-four hours or more before the experiment is begun. Xylene is carefully applied with a cotton applicator to local areas of the skin at varying intervals before 10 cc. of a 0.2 per cent solution of trypan blue is given intravenously.

The skin in the normal adult rabbit becomes hyperemic thirty to sixty seconds after the local application of xylene. Edema also quickly appears. The macroscopic evidence of inflammation usually persists for four or five days. Intravenously injected trypan blue localizes and concentrates in the xylene-treated areas only during a specific interval.¹ Essentially the same amount of dye concentrates in xylene-treated areas as in the untreated areas of the skin when the irritant is applied three hours or longer before the dye is given. The largest amount of dye localizes and concentrates in the xylene-treated area when the irritant is applied immediately before the dye is injected. There is a progressive diminution in the quantity of dye that localizes and concentrates in xylene-treated areas when the interval between the application of the irritant and the intravenous injection of the dye is progressively increased.

Sixteen rabbits with staphylococcic septicemia were used to study the localization and the concentration of trypan blue in xylene-treated areas of the skin.

4. Rigdon, R. H.: Localization of Staphylococci in Areas of Inflammation Produced by Xylene, *Arch. Surg.* **41**:879 (Oct.) 1940.

5. Rigdon (footnotes 1 a, 3 c and 4). Cressman and Rigdon.^{3b}

The animals were given 10 cc. of a heavy suspension of staphylococci in a solution of sodium chloride. Xylene was applied, and trypan blue was given to 7 of these rabbits within two hours after the injection of the bacteria. The macroscopic reaction, the time of reaction and the quantity of dye that localized and concentrated in the skin were the same as with normal adult rabbits.

In 9 rabbits xylene was applied from three to eight hours after staphylococci were injected. This delay in the application of xylene was made to see whether animals sick with staphylococcic septicemia reacted the same as normal rabbits. The general appearance of these 9 rabbits varied widely at the time the xylene was applied. Hyperemia and edema occurred in some of these rabbits after the application of xylene, exactly as it does in normal animals. In some rabbits, however, there was either a diminution or a complete absence of hyperemia after the application of xylene. The case of rabbit 739 illustrates the failure of hyperemia to occur:

- 9:30 a. m. 10 cc. of a suspension of staphylococci in a solution of sodium chloride given intravenously.
- 5:30 p. m. Xylene applied to area 1.
- 5:45 p. m. Xylene applied to area 2; the rabbit was sick and too weak to stand.
- 6:00 p. m. Xylene applied to area 3.
- 6:15 p. m. Xylene applied to area 4; there was no hyperemia or edema in the xylene-treated areas.
- 6:15 p. m. 10 cc. of trypan blue given intravenously; the rabbit died.

There was also a variation in the time of reaction and in the quantity of trypan blue that localized and concentrated in the xylene-treated areas of the skin in the rabbits which were sick after the injection of staphylococci. The case of rabbit 740 illustrates the failure of trypan blue to localize and concentrate in xylene-treated areas:

- 9:30 a. m. 10 cc. of a suspension of staphylococci in a solution of sodium chloride given intravenously.
- 5:30 p. m. Xylene applied to area 1.
- 5:45 p. m. Xylene applied to area 2.
- 6:00 p. m. Xylene applied to area 3.
- 6:05 p. m. The skin was hyperemic in areas to which xylene had been applied.
- 6:15 p. m. Xylene applied to area 4; 10 cc. of trypan blue given intravenously.
- 6:25 p. m. No dye in any of the xylene-treated areas.
- 6:27 p. m. The rabbit was too weak to stand.
- 6:40 p. m. A reddish brown color was present in the areas of the skin treated with xylene.
- 6:37 p. m. Rabbit died; no dye localized in any of the xylene-treated areas.

It was difficult to control this experiment since the reaction to the inoculation of staphylococci varied in the different rabbits. It may be concluded from these experiments, however, that the skin reaction to xylene and the localization

of trypan blue in xylene-treated areas in the animals given staphylococci vary from those in normal adult rabbits.

LOCAL INFLAMMATORY REACTION IN THE SKIN OF RABBITS WITH STAPHYLOCOCCIC SEPTICEMIA

Eighteen rabbits were used. Xylene was carefully applied with a cotton applicator to small areas of skin at intervals of six, four and two hours before the

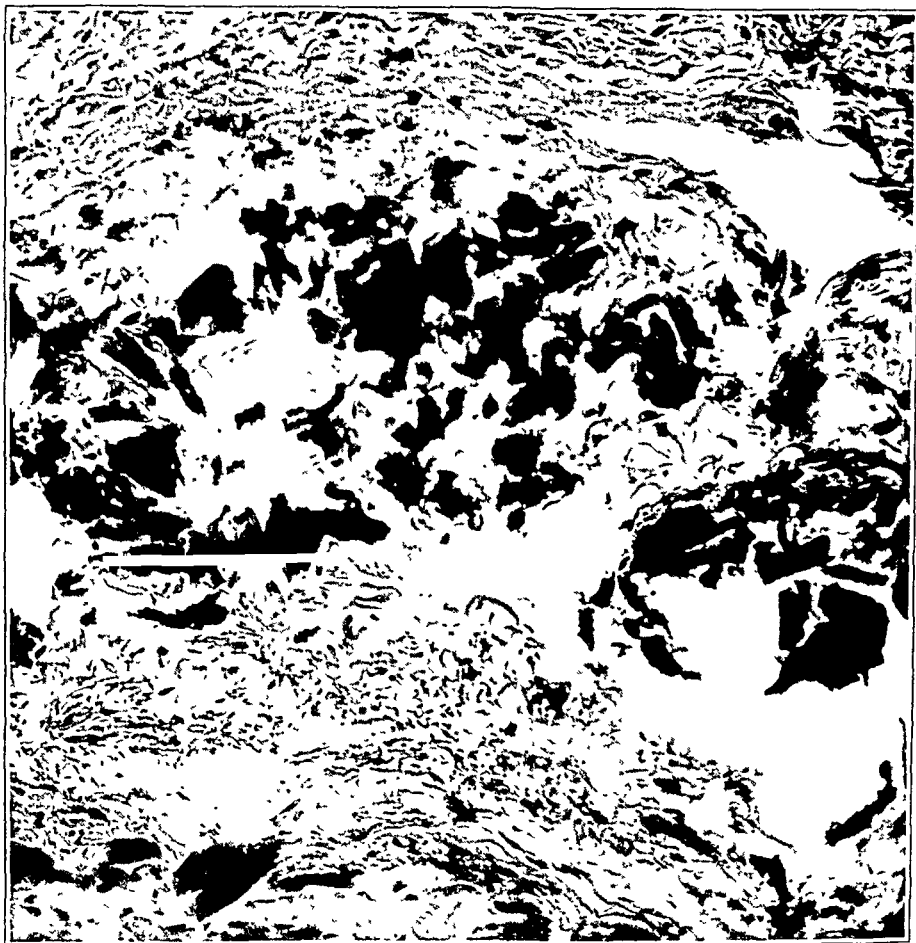


Fig. 1.—This rabbit (332) was given 10 cc. of a heavy suspension of staphylococci in a solution of sodium chloride intravenously and, immediately thereafter, 0.2 cc. of a 2 per cent suspension of aleuronat intradermally. It was killed six hours later. There were no leukocytes infiltrating the particles of aleuronat.

animals were killed. Two tenths of a cubic centimeter of a heavy suspension of staphylococci in a solution of sodium chloride and a similar amount of a 2 per cent suspension of aleuronat in a solution of sodium chloride were injected intradermally in different areas at the same time that xylene was applied. The bacteria had been grown on the surface of infusion agar and had been washed and suspended in a solution of sodium chloride.

Five of the rabbits were given 10 cc. of a heavy suspension of staphylococci in a solution of sodium chloride intravenously at the beginning of the experiments. There was marked diminution of hyperemia where xylene was applied and bacteria and aleuronat were injected intradermally. In 4 of the rabbits given staphylococci intravenously there were essentially no leukocytes in either the areas of the skin where xylene was applied or around the particles of aleuronat and the bacteria. There were only a few leukocytes about the irritants in 1 of the rabbits in this group. In the 13 control animals there were many leukocytes in the area to

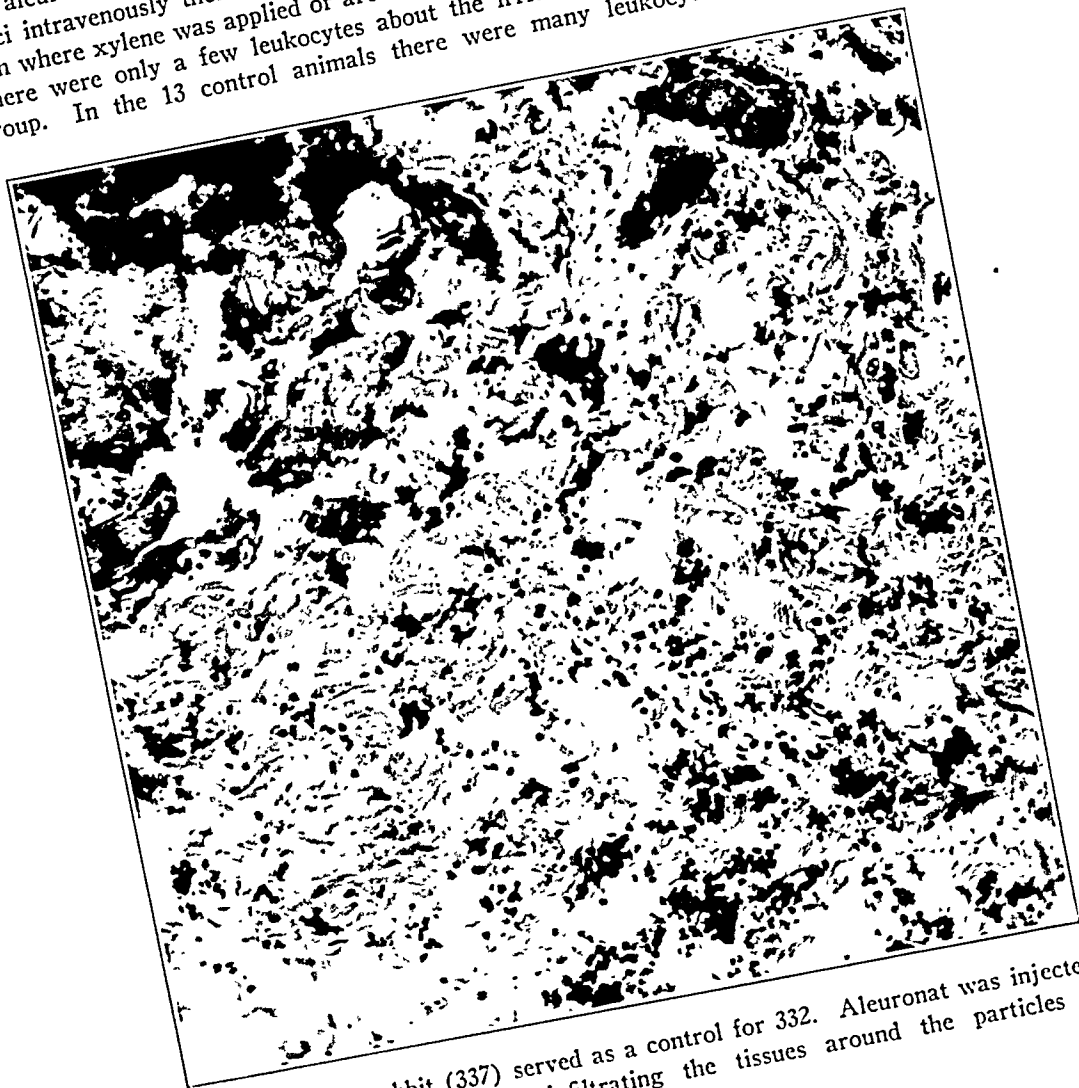


Fig. 2.—This rabbit (337) served as a control for 332. Aleuronat was injected. There were many leukocytes infiltrating the tissues around the particles of aleuronat.

which xylene was applied and in which staphylococci and aleuronat were injected (figs. 1 and 2).

A second group of 7 rabbits were given a similar quantity of aleuronat and a corresponding number of staphylococci intradermally. The injections were made at intervals of six, four and two hours before the rabbits were killed. Five of the rabbits were given intravenously 10 cc. of a heavy suspension of staphylo-

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cocci in a solution of sodium chloride. Three of these rabbits did not show any leukocytes about the staphylococci and aleuronat, while 1 animal had only a few cells. The fifth rabbit had essentially the same number of leukocytes as the 2 control animals (fig. 3).

A third group of 7 rabbits were given intradermal injections of 0.2 cc. of a heavy suspension of staphylococci in a solution of sodium chloride. At the same time they were given 10 cc. of the same suspension intravenously. These rabbits

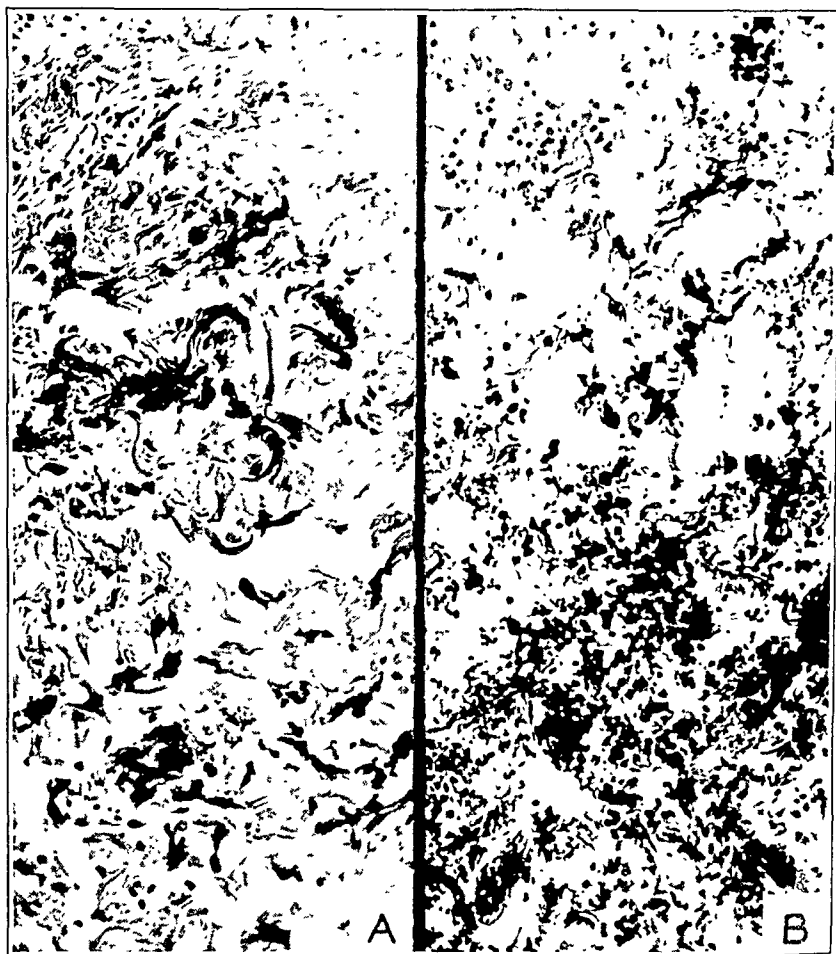


Fig. 3.—*A*, this rabbit (328) was given 10 cc. of a heavy suspension of staphylococci in a solution of sodium chloride intravenously and, immediately thereafter, 0.2 cc. more intradermally. It was killed six hours later. There were no leukocytes infiltrating the tissues around the groups of bacteria. *B*, this rabbit (337) served as a control for 328. Many leukocytes were infiltrating the tissue into which the bacteria had been injected.

were killed two hours later. No leukocytes were present in the tissues about the bacteria.

It is evident from these observations that polymorphonuclear leukocytes do not localize and concentrate around staphylococci and aleuronat and in the corium

in the areas to which xylene is applied when rabbits are given 10 cc. of a heavy suspension of staphylococci in a solution of sodium chloride intravenously before the application or the injection of the irritants.

TOTAL NUMBER OF WHITE BLOOD CELLS IN THE CIRCULATING
BLOOD AFTER THE INTRAVENOUS INJECTION OF
STAPHYLOCOCCI

The observations in the preceding experiment showed that polymorphonuclear leukocytes fail to localize and to concentrate about staphylococci and aleuronat when they are injected intradermally into rabbits previously given a heavy suspension of staphylococci in a solution of sodium chloride intravenously. In view

*White Blood Cells in the Peripheral Blood of Rabbits Given
Staphylococci Intravenously*

Rab- bit	Control Average Number of White Cells	Time Staphylo- cocci Were Given Intrave- nously	Time and Number of White Blood Cells in Peripheral Blood						Death	
			10 a.m.	11 a.m.	12 m.	1 p.m.	2 p.m.	3 p.m.	Time	Manner
482	8,800	9:05 a.m.	15,650	2,050	3,800	4,750	1,850	3,750	3:45 p.m.	Died
484	8,462	9:05 a.m.	13,750	10:45 a.m.	Died
485	7,750	9:05 a.m.	3,750	2,000	3,550	3,050	1:30 p.m.	Died
486	9,725	9:05 a.m.	15,500	6,750	11,050	5,400	1:30 p.m.	Died
487*	7,025	10:00 a.m.	2,800	1,900	1:30 p.m.	Killed
488*	6,700	10:00 a.m.	40,800	3,650	1:30 p.m.	Killed
490*	6,625	10:00 a.m.	3,100	2,100	1:30 p.m.	Killed
491*	6,425	10:00 a.m.	4,000	2,750	1:30 p.m.	Killed
492*	7,327	10:00 a.m.	3,250	5,400	1:30 p.m.	Killed

* These rabbits were given an intradermal injection of 0.2 cc. of the suspension of staphylococci at 11:30 a. m. No leukocytes were present about the staphylococci in the skin in any of these rabbits. Xylene was applied to an area of the skin of each of these rabbits, and 10 cc. of trypan blue was given intravenously to make possible a study of capillary permeability. The dye localized the saline in the xylene treated areas as it does in normal rabbits.

of this observation the number of leukocytes in the circulating blood of similarly treated rabbits was studied.

Standard technic was used in obtaining and counting the white blood cells. Blood was obtained from the ears. The interval between the injection of the bacteria and the time the blood was taken for the counts is shown in the table. The data were obtained from a group of 9 adult rabbits given a heavy suspension of staphylococci intravenously. Leukopenia developed in these rabbits within an hour.

The following experiment was made to determine the effect of various dilutions of staphylococci on the number of white blood cells. A suspension of staphylococci in a solution of sodium chloride was injected into 4 rabbits intravenously, and the leukocytes were counted. The same volume of a suspension of staphylococci in a solution of sodium chloride, in which, however, the number of bacteria represented a 1 to 3 dilution, was injected intravenously into a second group of 4 rabbits. The result of this experiment is shown in figure 4. The

number of circulating leukocytes in this experiment was apparently influenced by the number of staphylococci injected. Death occurred more quickly in the group given the heavy suspension than in the group given the lighter inoculum. The staphylococci apparently multiplied after injection, and accompanying this multiplication there occurred leukopenia, as shown in figure 4. When the heavy suspension was used, leukopenia occurred immediately and persisted until death. When a light suspension was injected, leukocytosis was sometimes followed by leukopenia which persisted until death.

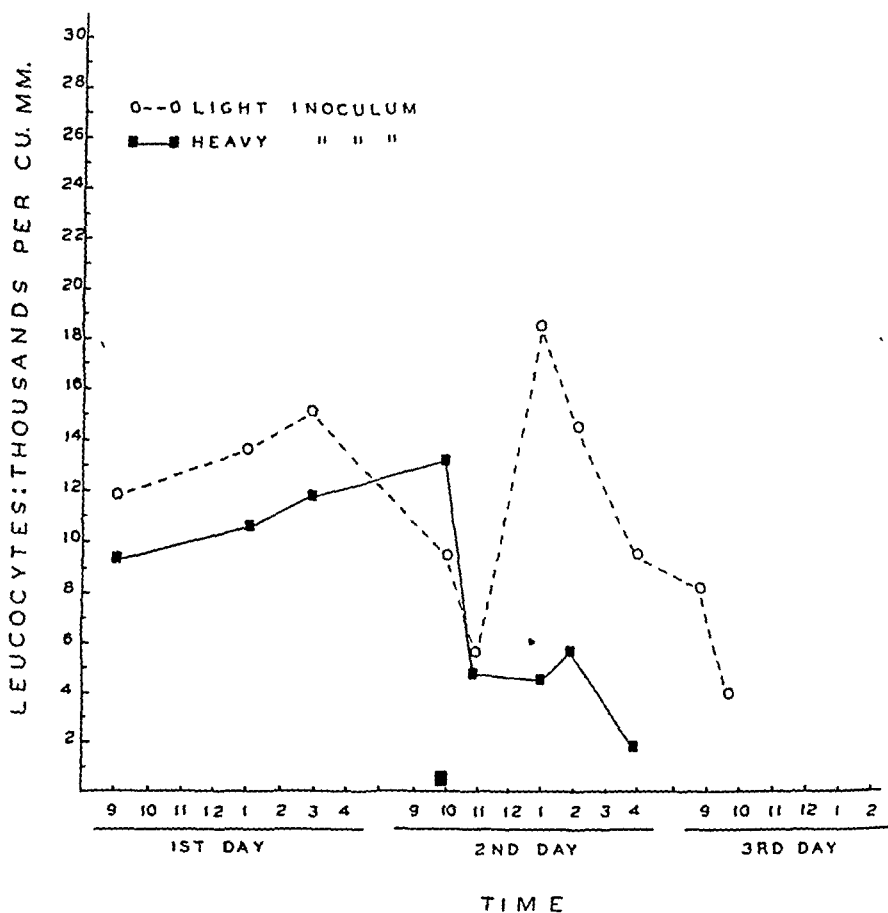


Fig. 4.—The white blood cell count in 8 rabbits (4 in each group) given 10 cc. of a suspension of staphylococci in a solution of sodium chloride intravenously. The light inoculum represents a dilution of 1 to 3 of the heavy inoculum. All rabbits given the latter were dead by 5 p. m. Those given the light inoculum survived for a longer period. However, all were dead twenty-eight hours after the injection of the bacteria.

COMMENT

These experiments show that both the macroscopic and the microscopic reactions in the skin of rabbits sick with staphylococcic septicemia vary from those in the skin of the normal rabbit. The reactions of the rabbits sick with staphylococcic septicemia are similar to those of animals given

alcohol and ether and resemble the reactions that may occur in rabbits given large injections of epinephrine.³

The vascular response to an irritant may be completely absent in the skin of the rabbit with staphylococcic septicemia. This vascular phenomenon may be associated with the fall in the blood pressure which may accompany septicemia. Blalock,⁶ in discussing acute circulatory failure, stated that "many different factors may enter into the production of shock that is associated with operations. Among these may be included hemorrhage, infection, anaesthesia, and particularly the disease for which the operation is performed."

The absence of polymorphonuclear leukocytes around the staphylococci and the particles of aleuronat in the skin of rabbits suggests the possibility either that there is a deficiency in the number of leukocytes in the circulating blood or that some inhibitory process has occurred to prevent the localization of these cells in the area of the irritants. The observations made in this study as well as those of Ewing⁷ indicate that leukopenia may follow the intravenous injection of staphylococci in the rabbit. It would seem from this study, however, that there are a sufficient number of white blood cells in the blood for at least a few to localize around the staphylococci in the skin. It appears more likely that the circulation in the small blood vessels in the skin is either diminished or completely absent in rabbits with severe staphylococcic septicemia. This appears likely in view of the complete absence of white blood cells around the staphylococci and the particles of aleuronat and the failure of trypan blue to localize and concentrate in xylene-treated areas of the skin. The leukocytes are inhibited from reaching the site of injury by the presence of this vascular constriction. In the study of capillary permeability and inflammation in rabbits given epinephrine it was suggested that the inhibition in the development of inflammation may be accounted for by vascular constriction.^{3c}

It will be shown in subsequent publications that a similar inhibition in the development of an inflammatory reaction may accompany loss of blood by bleeding and also severance of the spinal cord in the adult rabbit.

The results obtained in this study show that a small number of staphylococci injected intravenously may cause leukopenia which is followed by leukocytosis. After this leukocytosis there occurs leukopenia which persists until death. Certain bacteria may fail to produce any change in the number of leukocytes; the number of bacteria, their virulence and the resistance of the host must be remembered.

6. Blalock, A.: *Acute Circulatory Failure as Exemplified by Shock and Hemorrhage*, Surg., Gynec. & Obst. **58**:551, 1934.

7. Ewing, J.: *Toxic Hypolencocytosis*, New York M. J. **61**:257, 1895.

SUMMARY

Capillary permeability and inflammation as observed in the skin of the rabbit after the injection of trypan blue vary in the animal with staphylococcic septicemia as compared with the normal rabbit. This variation apparently may be associated with constriction of the small blood vessels in the skin.

The reaction to xylene, staphylococci and aleuronat in rabbits with staphylococcic septicemia is similar to that which may occur in rabbits anesthetized with alcohol or ether or given large quantities of epinephrine.

REDUCED TEMPERATURES IN SURGERY

II. AMPUTATIONS FOR PERIPHERAL VASCULAR DISEASE

LYMAN W. CROSSMAN, M.D.

WILFRED F. RUGGIERO, M.D.

VINCENT HURLEY, M.D.

AND

FREDERICK M. ALLEN, M.D.

NEW YORK

One of us (F.M.A.)¹ has suggested possible surgical uses of cold on the evidence of animal experiments and a few clinical cases. Since the adoption of this method as a routine in City Hospital, sufficient clinical evidence has been accumulated to permit an evaluation of the results. This paper gives (1) the reports of 9 cases, in which fatalities, partial successes or difficulties encountered in the early experience are represented, and (2) a table of the results in the entire series of 45 cases to date. The majority of the cases belong to the initial period in which ice or ice water was used for chilling. In the later cases a special refrigerating apparatus has been used in the preparation of patients for operation, producing the same effect more conveniently.

REPORT OF CASES .

CASE 1.—A Russian Jewish peddler aged 82 years was admitted Jan. 8, 1941 with arteriosclerosis. The general history was noncontributory, and he had used no alcohol or tobacco. For one year he had been unable to stand for any length of time because of pain in both feet. The pain increased, and discoloration began a short time before admission. The salient observations in the examination were as follows: The temperature was 100.2 F. The blood pressure was 115 systolic and 80 diastolic. The urine and the chemical composition of the blood were normal. There was atrophy of the tissues of both legs from the knees down and black gangrene of all the toes of both feet. Pulsation was absent in the popliteal arteries and everywhere below. There was coldness to touch beginning at the middle

From the Surgical Division, City Hospital.

This study was aided by a grant from the Council on Physical Therapy of the American Medical Association.

1. Allen, F. M.: (a) Local Asphyxia and Temperature Changes in Relation to Gangrene and Other Surgical Problems, *Tr. A. Am. Physicians* **52**:189, 1937; (b) Reduced Temperatures in Surgery: I. Surgery of Limbs, *Am. J. Surg.* **52**: 225, 1941.

of the dorsum of the right foot and about the middle of the left calf; in the left leg there were dusky red streaks from the gangrenous area up to the knee.

Operation was advised but refused until January 12, when the entire left foot was dark colored; the streaks of lymphangitis extended above the knee joint, and the temperature was 102 F. The leukocyte count was 22,000 with 81 per cent polymorphonuclears and 30 per cent young forms.

Prior to operation on January 12, $\frac{1}{6}$ grain (0.01 Gm.) of morphine sulfate and $\frac{1}{150}$ grain (0.0004 Gm.) of scopolamine hydrobromide was given hypodermically because of the patient's apprehension and nervousness but had no visible effect. A tourniquet consisting of two turns of pure gum tubing was applied a little below the middle of the left thigh, tightly enough to stop the arterial flow. The head of the bed was elevated; the leg was placed on a layer of cracked ice in a rubber sheet and then completely buried in ice up to several inches above the tourniquet. The melting ice drained into a bucket beside the bed. The patient, with the ice still on his leg, was carried to the operating room in time to start the operation two hours after the beginning of refrigeration. He was placed on the operating table without ice, and the operative field was painted with tincture of zephiran.² The procedure was an amputation through the lower part of the thigh after a method to be described later. No drainage was used.

The patient had eaten a regular meal before the operation and experienced no discomfort. The blood pressure ranged from 105 systolic and 80 diastolic before the operation to 130 systolic and 90 diastolic during the operation and at the end. The pulse and respiration rates did not change.

The wound was lightly dressed, and ice bags were applied continuously. No signs of shock were seen in the subsequent condition or behavior of the patient. By the next day the temperature had fallen to 99.5 F. On the second day there was a return of fever, complaints of dyspnea and suggestive signs in the lung; all of these cleared up after the administration of sulfathiazole (2-[paraaminobenzene-sulfonamido]-thiazole). On the seventh day after operation the sutures were removed, and about 25 cc of odorless discharge was expressed from one angle of the wound.

During the days immediately following the operation a dark violet discoloration extended rapidly over the right foot. Consent for a second amputation was not obtained; ice bags were therefore used continuously to keep this foot at almost ice temperature. The spread of gangrene and infection was thus apparently delayed, and the good general condition indicated absence of septic absorption, but there was no tendency toward healing or demarcation.

On January 21 (nine days after the first operation) the entire right foot was so dark in color that the patient accepted amputation. The methods were essentially the same as in the first operation, and the procedure resulted in primary union.

Although both stumps were seemingly in excellent condition, there were occasional moderate elevations of temperature, not to be explained by lack of response to sulfathiazole. Appetite and strength slowly failed, though the fever subsided. January 31 seemed to mark a turn for the better, with continued good condition of the wounds, a normal temperature and the return of appetite and spirits, but death occurred that night during sleep.

2. Zephiran is alkyl dimethylbenzyl-ammonium chloride. It is a cationic detergent having about the same consistency and physical properties as liquid soap, which is an anionic detergent.

The apparent lack of disturbance from two thigh amputations in a senile patient seems to illustrate the shock-saving character of the procedure. The death may reasonably be attributed to delayed shock, which has been discussed elsewhere,¹ and to the general strain of wound healing and minor degrees of lingering infection. The patient's strength might have been better preserved if earlier consent for amputation could have been obtained.

CASE 2.—A German housewife was admitted Jan. 15, 1941 with diabetic gangrene. Her age was given as 64 years, but her appearance suggested a greater age. The diabetes was of uncertain duration, but she had recently had polyuria and loss of weight. Five months before, she had stubbed her foot against a bed. All the toes turned dark; the first and fifth progressed to gangrene, while the others cleared up. The pain and the black area extended slowly, and a spot of gangrene also appeared on the heel.

Examination showed auricular fibrillation and systolic and diastolic murmurs over the entire precordium; these were attributed to rheumatic heart disease. In addition to the gangrene there was absence of pulsation in both popliteal arteries and below. Glycosuria and hyperglycemia were cleared up under treatment by the metabolic service of City Hospital (Dr. J. F. Hart). Operation was refused, while the temperature ranged from 100.6 to 102.8 F., until January 20, when reddish streaks extended up to the knee and the temperature rose to 104 F. Amputation was then finally accepted and was performed the same day.

A narrow tourniquet was applied at the midthigh, and the leg was packed in ice to a little above this level for one and three-quarters hours. The operation was similar to that performed in case 1. The refrigeration proved to be too brief for perfect anesthesia in the thigh, because a slight and delayed sensation was felt when the sciatic nerve was cut. However, there was no important discomfort. The deep tissues were closed with fine chromic gut, and the skin with silk suture, without drainage. The blood pressure ran without important change to a little above and below 90 systolic and 50 to 60 diastolic.

The dressing was limited as usual to a few layers of gauze, and three ice bags were kept around the stump. The temperature fell within twenty-four hours to 99.8 F. Eight days after operation all sutures were removed; with refrigeration, this was too early. One corner of the wound was opened slightly; pink tissue was revealed, and about 5 cc. of serous fluid escaped. Otherwise, healing was satisfactory, without edema or dark color. On the ninth day after operation the patient seemed well enough to sit up in a wheel chair, but she died suddenly of heart failure.

The amputation was borne without signs of shock or the interruption of eating and other habits in the presence of a cardiac complication which was evidently severe according to both the examination and the termination.

CASE 3.—An Italian street cleaner aged 72 years was admitted Jan. 21, 1941 with diabetic gangrene. There was a wedge-shaped area of black gangrene proximal to and including the second, third and fourth toes of the left foot and with edema of the entire foot up to the ankle. The history was vague, except that ulceration had begun in October 1940, that he had received insulin and other

treatment in another hospital but had refused amputation and signed himself out on December 8. The salient observations in the examination were as follows: There was pallor of the skin. In one eye there was a cataract, and in the other iridectomy had been done. There was moderate atrophy of the legs below the knees. The pulse was strong in both popliteal arteries, but it was not palpable in the dorsalis pedis or the posterior tibial arteries. Oscillometry confirmed these observations. The temperature was 100.5 F. The urine contained sugar (4 plus) and acetone (1 plus). The blood sugar was 236 mg. The hemoglobin content was 80 per cent. The leukocyte count was 20,000, with 85 per cent polymorphonuclears.



Fig. 1.—Ice water preparation for operation for a patient able to sit up.

Under the care of the metabolic service of City Hospital the blood sugar was made normal within twenty-four hours, and some hypoglycemic reactions were checked with dextrose. Oliguria was treated with intravenous infusions. A tourniquet was applied in the upper part of the calf and the leg placed in chopped ice to a little above this level. The operation was unexpectedly delayed and actually began after four and one-half hours of refrigeration. Amputation was performed in the lower third of the tibia. There was a slight trickle of blood from the tibial marrow in spite of the tourniquet. After the tourniquet had been removed and the bleeding points tied, it was found that the scanty soft tissues could not be closed over the bone ends without the risk of tension. Therefore both bones were sawed off again at a slightly higher level. The wound was closed

without any complaint of pain and without drainage. The systolic blood pressure ranged between 110 and 120 throughout, except for one brief elevation to 150.

After operation, ice bags were applied outside thin dressings. The temperature fell during the night to 99.5 F. and rose the following day to 104 F. A transfusion of 500 cc. of blood was given. The temperature continued high until January 25 and then subsided. Chilling of the stump was irregular. It is uncertain whether too high or too low temperatures were responsible for the formation of superficial blebs, which were followed by necrosis. When all plans had been made for reamputation, extreme intoxication developed overnight so that operation was impossible. On the eighth postoperative day (January 29) a tourniquet was applied and the leg refrigerated, but death occurred within a few hours.

There is as yet no accurate knowledge of the duration of anesthesia after removal of the tourniquet. In this instance it was sufficient for a reamputation of bones, but it may vary with the duration of the preceding refrigeration and with the existing temperature.

Continuance of ice temperature and tourniquet pressure for four and one-half hours may be suspected as contributing to the bad result through damage to tissues or blood vessels, but other experience seems to exclude this factor and to prove that much longer continuance is still safe.

Death might have been preventable by better regulation of the postoperative temperature, by the use of drainage, by a higher initial amputation or a prompter reamputation or by correction of other possible errors due to inexperience.

CASE 4.—A Negro carpenter aged 51 years was admitted Jan. 4, 1941, with arteriosclerotic gangrene. The temperature was 99.5 F., and the general condition was good. Pain in the small toe of the right foot had begun six months before and grown steadily worse, and ulceration had gradually followed. Examination showed blood pressure of 180 systolic and 100 diastolic and a moderately enlarged heart. Both legs were atrophic below the knees. No pulsations were palpable in the popliteal arteries or below. Oscillometer waves were slight in the thigh, were barely traces below the knees and were absent lower. Roentgenograms showed marked calcification, especially from the knees downward. The small toe of the right foot was black and mummifying, and there was a large black ulcer on the dorsum over the fourth and fifth metatarsal bones. The entire foot was swollen and cyanotic, but roentgenograms revealed no osteomyelitis. During ten days the condition grew worse under routine treatment, including continuous covering with a cradle containing one 10 watt electric bulb. There was extension of the black ulceration, pain, tenderness and swelling. Sleep was not obtained with morphine or other sedatives. Dusky red streaks followed the veins as high as the ankle, and the temperature showed slight elevations to 100.8 F. The patient was reluctant to accept amputation but finally consented to have the foot alone removed.

On January 14 a tourniquet was applied to the calf, and the leg was immersed in ice water to a level of a few centimeters above the tourniquet for one and three-quarters hours. Amputation was done, slightly above the ankle joint, with closure of the skin without drainage.

Before and during the operation the pulse rate ranged from 105 to 110 and the blood pressure between 145 and 160 systolic and 95 and 105 diastolic. The patient ate a comfortable meal immediately after returning to the ward. With the relief of pain, he slept for eighteen hours.

Subsequently he found the cold uncomfortable and drew his stump away from the ice bags whenever he was not watched. At the time the dressings were done, once or twice daily, the stump was found warm, edematous, cyanotic and tender, and the wound edges showed a narrow zone of dark slough. The temperature rose to 102 F., and though there were no chest signs, sulfathiazole was given. When the patient became aware of the threatening condition of the stump and was convinced by his own observations that it appeared better when cool, he

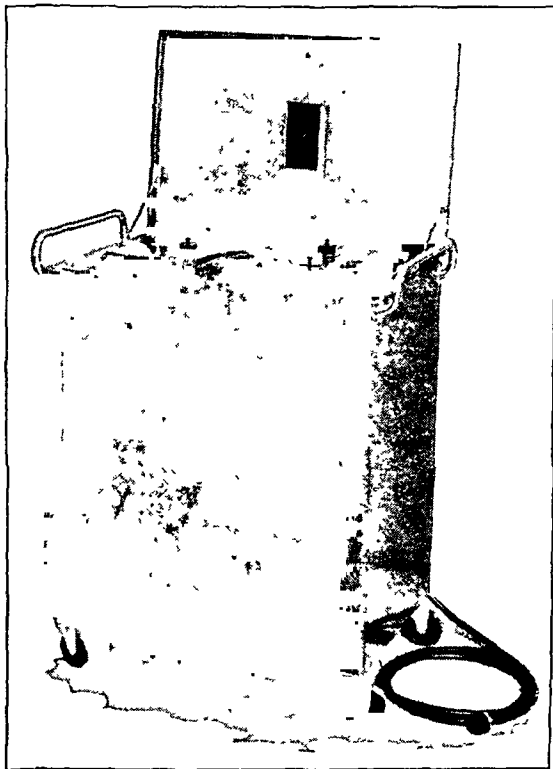


Fig. 2.—Electric unit which provides circulation for applicators which maintain any desired constant temperature about a limb.

declared that the coolness was comfortable and thereafter cooperated in retaining the ice bags. Notwithstanding improved appearances, the damage already done was sufficient to necessitate reamputation.

This amputation, between the middle and upper thirds of the tibia, was performed on February 2 by the same tourniquet-refrigeration method. Two drains of gutta-percha tissue were placed in the wound. The flaps were not full enough for the large bone, so that the tension was commented on at the time of closure. With the postoperative use of ice bags nothing more was noticeable for about a week; then a narrow zone gradually became necrotic, and all sutures were removed. This sufficed to arrest the necrosis. The temperature rose to about 102 F. without malaise. The soft tissues were left practically flush with the end of the bone

but no healing occurred. Bronchopneumonia and death seemed imminent, when amputation through the lower part of the thigh was accepted and followed by primary union.

Refrigeration seems to favor healing with a low amputation. There was a psychologic advantage in that operation was accepted sooner than if the patient had been confronted with a thigh amputation. There was a physical advantage in that repeated operations could be performed without any apparent disturbance of the patient's feelings or habits.

CASE 5.—A German janitor aged 68 years was admitted on Jan. 2, 1941 with diabetic gangrene. The temperature was normal, and the general condition was good. Fifteen years earlier he had lost the nail of the great toe of his right foot because of a blow on it, and in the course of treatment he was told that he had severe diabetes. He was given a diet and insulin but abandoned them as soon as the toe was well. His condition then ran the usual course of mild diabetes, with good nutrition and feelings, a familiar prelude to complications. Two years before admission to City Hospital he was in a hospital because of weakness; again a diet and insulin were prescribed, but he again discarded them on discharge and continued to keep good weight and apparent health. Three months before admission a painful ulcer developed on the sole of his left foot and gradually enlarged. For the past two months he had been taking 15 units of insulin, twice daily. With this he felt well, but the sugar was not controlled, and the ulcer continued to progress.

Examination showed bilateral cataracts and marked arteriosclerosis, with good nutrition and blood pressure 120 systolic and 60 diastolic. The legs were atrophic below the knees. Oscillometric waves were only slightly reduced below both knees but were small above the left ankle and absent above the right ankle. The left foot, however, had a deep painful ulcer in the metatarsal region of the sole, and there was a corresponding purplish discoloration on the dorsum.

Hyperglycemia and glycosuria (4 plus) were present without acetone. The diabetic condition was treated in the metabolic service of the City Hospital; it was controlled with a diet and an increase of insulin to 55 units daily. In spite of this and local measures, the gangrene slowly extended. On January 14 consent was finally obtained for operation. With full realization of the odds against any conservative attempt, it was decided to make a trial, at least for the instructiveness.

Therefore, on January 14 a narrow tourniquet was applied above the ankle, and the foot was immersed in ice water to a level a little above this for one and one-half hours. The patient ate part of his lunch while waiting outside the operating room and the remainder after the end of the operation. By removal of the second and third toes and the ends of the corresponding metatarsal bones it was possible to eliminate the gangrenous area, although there was a dangerous encroachment on the fourth toe and its metatarsal. Only slight bleeding needed to be checked after release of the tourniquet. The skin and the soft tissues could not be approximated but were drawn slightly together with silk. The blood pressure was 158 systolic and 80 diastolic before the operation, probably from nervousness, but it soon fell and remained at 130 systolic and 64 diastolic.

The usual light dressing and ice bags were applied, but the patient was unruly and managed to keep his foot warm most of the time. The interior of the wound became a black sloughing mass. Healing was impossible, and consent for amputation was obtained.

On February 1 the leg was refrigerated, and amputation was performed through the lower third of the tibia. Two soft rubber drains were used. The patient's psychic state resulted in irregular postoperative cooling with the ice bags in place only part of the time. A part of the wound healed by first intention; there was a superficial slough laterally which on separation left a clean granulating surface.

The production of any real suffering by cold is a reason for omitting refrigeration or for proceeding with great care, but this and the preceding case illustrate mishaps due entirely to psychic difficulties. It remains unknown whether healing could have been obtained by efficient cooling after the ultraconservative first operation in such a case, but there is no doubt that cold assisted in checking tissue breakdown and infection. The



Fig. 3.—Recent supracondylar amputation done with refrigeration and higher amputation performed two years previously by older method.

final operation illustrates healing under refrigeration in the customarily forbidden region of the lower part of the tibia.

CASE 6.—A Greek cook aged 66 years was admitted on Nov. 27, 1940 with arteriosclerotic gangrene and sepsis. He complained of pain in the legs which had progressively increased for six months. He had cramps in the legs in walking and had had a series of ulcers on the legs during the preceding six years; he had had injections for varicose veins three years before admission.

The findings on admission were: temperature, 101 F.; pulse rate, 120; blood pressure, 178 systolic and 96 diastolic; urine and chemical composition of the blood, normal. The right leg showed numerous pigmented scars of old ulcers. The left leg was atrophic and indurated; a dirty ulcer covered two thirds of the medial and posterior surfaces and exposed the achilles tendon.

Septic temperatures persisted despite treatment, and the constitutional condition was serious. On account of good pulsations and oscillometric readings at and

below the knee, it was decided to perform amputation through the calf muscles. This was done on December 19 with the patient under anesthesia induced with a morphine salt and scopolamine hydrobromide and with the site of operation under local anesthesia induced with procaine hydrochloride. The flaps were closed with a drain, which was removed after twenty-four hours. Sloughing followed.

All these events occurred in another surgical service, and on transfer of service the patient was found with the bones of the knee exposed and purulent infection extending above the joint. His temperature ranged from 97.5 to 101 F., with a disproportionately high pulse rate. The hemoglobin content was 76 per cent. The leukocyte count was 10,000, with 76 per cent polymorphonuclears. The patient was considered moribund and unfit for operation.

As the refrigeration method had just been adopted, it was applied in this case by surrounding the stump with bare ice bags to reduce the skin temperature to almost freezing. Immediately the discharge was reduced to about a tenth of the previous quantity, and the local and general conditions showed marked improvement within twenty-four hours. This immediate result with refrigeration was obtained after three days of the administration of sulfathiazole had shown no perceptible effect. A blood transfusion was then given, and on the next day (January 21) a tourniquet was applied at the mid thigh and ice packed about the limb for two and one-half hours. Amputation was then performed in the lower third of the thigh, barely above the uppermost pocket of visible pus. The edges were drawn together only partially, leaving plenty of open drainage space. After operation, thin dressings and continuous application of ice bags were employed. The patient was immediately comfortable and gained rapidly in strength and appetite. The exposed muscles remained pink and fairly clean, but with any attempt to withdraw the ice bags an unhealthy color and a foul discharge appeared.

Toward the middle of February, with the local condition and general strength still good, a slight elevation of temperature was explained by the finding of an indurated area high up on the posterior surface of the thigh. In lieu of any other treatment, an ice bag was applied to this area for the first time. Slowly a fluctuant area developed, and an incision was made almost to the ischial tuberosity. Slough and thin pus were evacuated, and after two weeks the clean granulating posterior surface of the thigh was covered with a skin graft.

Case 6 illustrates a type of trouble which is familiar under the customary surgical methods, also the service of the new method in avoiding shock and checking infection. With reference to preservation of tissue vitality, it is noteworthy that no sign of trouble developed in tissues which were made bloodless by the tourniquet at operation or which were later chilled with ice bags; the secondary infection occurred only above this zone.

CASE 7.—A Jewish building superintendent aged 49 years was admitted to a hospital with diabetic gangrene and infection. He gave a history of ten years of mild diabetes treated with diet only. Polydipsia and polyuria had long been present. One month before admission gangrene began in the left great toe and became steadily worse. The gradual increase of intoxication and fever was not checked by several courses of treatment with sulfanilamide and sulfathiazole. Finally, he was given insulin and transferred to City Hospital, with the diagnosis of an inoperable condition, on Jan. 31, 1941.

Examination showed a pale flabby obese man who was conscious and able to speak faintly and who complained of coldness and chills. There were coarse tremors of the extremities and cold perspiration. The temperature was 104 F. The pulse rate was 110 and extremely weak. The respiration rate was 28. The blood pressure was 100 systolic and 55 diastolic. The urine was free from sugar and acetone. The blood sugar was 105 mg. The Wassermann test was negative. The red blood cell count was 3,200,000; the leukocyte count was 11,000 with 92 per cent polymorphonuclears. A blood culture yielded no growth. The abdomen was pendulous and soft. All the viscera were normal. Palpable pulses were absent in both popliteal arteries and below. The left foot was swollen to nearly twice the normal size; multiple perforations in the sole discharged pus and slough. Edema diminished gradually up to the knee, and streaks of lymphangitis were visible up to the midcalf. Collections of yellow pus, rather extensive but superficial, also were present on the right ankle and the upper lateral aspects of both thighs.

An intravenous infusion of 1,000 cc. of physiologic solution of sodium chloride with 5 per cent dextrose was given without perceptible change in the condition. A tourniquet was applied just below the knee and the leg refrigerated as usual. The patient lost consciousness briefly whenever raised up or moved. After only one and one-half hours of refrigeration the leg was amputated a little below midcalf; a slight burning pain was experienced when the nerves were cut. In spite of marked thickening of the arteries, the tissues were bright colored and the blood supply apparently adequate, except on the medial aspect. Here a thick column of wet dark necrotic subcutaneous tissue extended to a level above the circular incision. It was trimmed out with scissors to a point about 2 inches (5 cm.) higher, where the dark color changed to a somewhat cooked appearance of the tissues. This pocket and the entire wound were packed with gauze soaked in cod liver oil. The usual ice bags were applied over light dressings.

At the time of beginning the operation the blood pressure had fallen to 65 systolic and 40 diastolic. A continuous record during the operation showed the maximum blood pressure to be 75 systolic and 50 diastolic, the minimum, 60 systolic and 42 diastolic, and the final, 65 systolic and 42 diastolic. After the operation a transfusion of 300 cc. of citrated blood was given, and subsequently another infusion of 1 liter of physiologic solution of sodium chloride with 5 per cent of dextrose, accompanied by 25 units of insulin was given subcutaneously. The patient was irrational at times during the night but drank some fruit juice and in the morning announced that he was feeling much better. His temperature was normal. The dressings were brightly stained with the serosanguinous discharge characteristic of refrigeration. The surface temperature of the stump was 23 C (73.4 F.). The administration of sulfathiazole was then begun with a dose of 4 Gm. followed by 1 Gm. every four hours.

With steady improvement the temperature remained normal except for unimportant elevations at times when pus was retained in the wound. The temperature of the stump was kept near 22 C. (71.6 F.). On February 7 the administration of sulfathiazole was discontinued. The blood pressure was 148 systolic and 88 diastolic.

The stump became clean, and healthy granulations appeared. Several superficial abscesses appeared on the trunk. After a two week period during which the patient had been in a chair, a chill appeared with a subsequent septic type of temperature. The urine was found to be loaded with pus. The patient now began

to go steadily downhill and twenty-four hours before death had a cerebral accident which caused loss of consciousness and right hemiparesis. Death occurred five weeks after amputation with a clean healing leg stump showing no evidence of local infection. There was no autopsy.

CASE 8.—An 83 year old man with senile arteriosclerotic gangrene was admitted on Feb. 3, 1941. Six months previously he had struck his right foot against a door, and it had remained painful thereafter. He was received by transfer from another hospital, where the great toe had been amputated. His temperature was 99.4 F. The pulse rate was 100. The respiration rate was 28. The blood pressure was 160 systolic and 0 diastolic. The blood and the urine were normal. The aortic second sound was accentuated. There were a few coarse rales at the bases of the lungs. General arteriosclerosis was marked; also marked was muscular atrophy, especially in the legs. No pulsations were palpable from either knee downward. There was profuse suppuration at the site of the missing right great toe, involving most of the sole. The dorsum was bright red, the entire foot was swollen to twice normal size, and streaks of lymphangitis extended a considerable distance up the calf. Amputation was performed immediately.

A tourniquet was applied close below the tubercle of the tibia, and the leg was refrigerated in ice for one hour. The amputation was done at about midcalf, within the area of evident lymphangitis. As the leg was thin, it seemed that the preparation would be easy; but although the tourniquet was tightly applied, it failed to overcome the bony protection of the artery. The usual bold circular cut caused a hemorrhage until the arteries were clamped, and because of the poor arrest of circulation the anesthesia was not perfect. The wound was closed with a small drain at each angle. The usual thin dressings and ice bags were applied, and a transfusion was given.

On subsequent days the ice bags were gradually reduced and the dressings made thicker, until on the sixth day all refrigeration was discontinued. Healing was by primary union, although it was slow. The flaps were long, and a posterior molded plaster splint helped to hold them in position.

There were several elevations in temperature to 101 or 102 F., apparently explainable by mild cough and rales in the lungs. In spite of some use of sulfathiazole, the attacks recurred, until on February 15 there was a more severe attack with a rise of the temperature to 104 F. Although the absence of consolidation was noted by roentgen and other examinations of the lungs, it is highly probable that the patient would have died except for a vigorous course of treatment with sulfathiazole, which produced a vivid rash and also an abrupt fall of the temperature to normal. Apart from this complication the patient was not appreciably disturbed by the operation and retained excellent appetite and spirits. The stump healed nicely, and after a period in a wheel chair he was discharged.

Delayed shock or the tax on the strength in connection with healing is the essential danger in a case such as this. Therefore, in addition to the shockless operation, the ability to restrict the amputation to a small part of the leg instead of a thigh appears to be an important advantage. The successful healing in the presence of arteriosclerosis, atrophy and infection gives encouragement concerning future possibilities under right management.

Data on Forty-Five Cases in Which Reduced Temperatures Were Used in Connection with Amputations for Peripheral Vascular Disease

Patient	Age, Yr.	Sex	Race	Disease	Local Condition	General Condition	Site of Amputation	Survival Period *
1	82	M	W	Diabetes and arteriosclerosis	Gangrene of both feet	Poor	Lower part of thighs (2)	21 days
2	61 (?)	F	W	Arteriosclerosis	Gangrene of foot	Fair	Lower part of thigh	14 days
3	72	M	W	Diabetes	Gangrene of foot	Poor	Lower part of leg	4 days
4	51	M	N	Arteriosclerosis	Gangrene of foot and leg	Fair	1. Lower part of leg 2. Higher part of leg 3. Lower part of thigh	
5	68	M	W	Diabetes and arteriosclerosis	Gangrene of foot	Poor	1. Foot 2. Midleg (closed)	
6	66	M	W	Arteriosclerosis	Gangrene of foot	Poor	7. Gastrocnemius muscle (Callander amputation) 2. Lower part of thigh 3. Incision and drainage 4. Skin graft	6 weeks
7	49	M	W	Diabetes	Gangrene of foot and infection	Very poor	Midleg (open)	
8	83	M	W	Arteriosclerosis	Gangrene of toes	Fair	Midleg (closed)	
9	72	F	N	Diabetes and arteriosclerosis	Gangrene of foot	Very poor	Lower part of thigh	6 days
10	67	M	W	Diabetes	Gangrene of foot	Fair	Midleg	
11	67	M	W	Diabetes (insulin resistant)	Gangrene of foot	Very poor	Midleg	5 days
12	50	F	N	Arteriosclerosis	Gangrene of foot and ankle	Fair	Midleg	
13	56	F	W	Embolism	Gangrene (?) of leg	Poor	Lower part of thigh	
14	65	F	N	Diabetes and arteriosclerosis	Gangrene of foot	Poor	Lower part of thigh	
15	79	M	W	Diabetes and arteriosclerosis	Gangrene of foot	Very poor	Lower part of thigh	
16	71	M	W	Arteriosclerosis	Pain	Fair	Midleg	
17	73	M	W	Diabetes and arteriosclerosis	Gangrene of foot	Poor	1. Midleg 2. Lower part of thigh	
18	83	M	W	Arteriosclerosis	Gangrene of foot	Poor	Midleg	
19	58	M	W	Diabetes and arteriosclerosis	Gangrene of foot	Poor	Lower part of thigh	
20	78	M	W	Diabetes and arteriosclerosis	Gangrene with infection	Very poor	1. Midleg 2. Lower part of thigh	
21	69	M	W	Diabetes	Gangrene of foot	Fair	Midleg	

22	74	M	W	Diabetes	Gangrene of foot	Fair	Midleg
23	50	M	W	Chronic osteomyelitis of foot and leg	Good	1. Midleg 2. Lower part of thigh
24	00	F	N	Diabetes	Gangrene of foot	Fair	Lower part of thigh
25	04	F	W	Diabetes	Gangrene of foot	Good	Midleg
26	57	M	W	Arteriosclerosis	Gangrene of foot	Fair	Lower part of thigh
27	03	M	W	Arteriosclerosis	Gangrene of foot	Fair	Lower part of thigh
28	76	M	W	Arteriosclerosis	Gangrene of foot	Very poor	Lower part of thigh
29	78	M	W	Diabetes and arteriosclerosis	Gangrene of foot	Very poor	1. Lower part of the right thigh 2. Lower part of the left thigh
30	71	F	N	Diabetes and arteriosclerosis	Gangrene of foot	Poor	Lower part of thigh
31	05	M	W	Diabetes	Gangrene of foot	Fair	Lower part of thigh
32	71	F	W	Diabetes and arteriosclerosis	Gangrene of foot	Poor	Lower part of thigh
33	60	M	W	Arteriosclerosis and frostbite	Gangrene of foot	Fair	Lower part of thigh
34	83	M	W	Arteriosclerosis	Gangrene of foot with infection	Fair	Midleg
35	85	M	W	Arteriosclerosis	Gangrene of foot	Poor	1. Midleg 2. Debridement for gas gangrene 3. Guillotine through the lower part of thigh
36	54	F	W	Diabetes, hyperthyroidism and arteriosclerosis	Gangrene of foot	Poor	Lower part of thigh
37	65	M	W	Diabetes	Gangrene of foot	Poor	Midleg
38	02	M	W	Syphilis, arteriosclerosis and old frostbite	Gangrene of foot	Fair	1. Amputation of toes 2. Midleg 3. Lower part of thigh
39	76	M	W	Arteriosclerosis	Gangrene of foot	Fair	1. Midleg 2. Lower part of thigh
40	72	M	W	Arteriosclerosis and diabetes	Gangrene of both feet	Poor	1. Lower part of the left thigh 2. Lower part of the right thigh
41	56	F	N	Arteriosclerosis	Gangrene of foot	Fair	Lower part of thigh
42	56	F	W	Diabetes	Gangrene of foot	Poor	Lower part of thigh
43	77	M	W	Arteriosclerosis	Gangrene of foot	Poor	Lower part of thigh
44	67	M	W	Arteriosclerosis and diabetes	Gangrene of foot	Good	Disarticulation at knee (amputation had been done through mid thigh on other side three years previously)
45	51	F	W	Diabetes	Gangrene of foot and ankle	Fair	Lower part of thigh

* Patients for whom no survival period is indicated are alive at the time of writing.

CASE 9.—The patient was a 73 year old Negress. She was received in poor condition but underwent an amputation through the lower part of the thigh with the usual absence of perceptible shock. Refusal of food during one week before operation was considered probably due to intoxication. Continued refusal after operation was also presumed at first to be temporary and largely psychic. As the stump remained in perfect condition and the entire picture was different from infection, the nature of the cachexia which proved fatal remained undetermined.

ANALYSIS OF DETAILS IN THE TABLE

A survey of the total series of 45 cases is given in the table. Thirteen of the patients were women. Seven of the patients were Negroes.

The major operations performed on the 45 patients numbered 57. All but 9 patients survive at the time of writing. Omitting 2 deaths at two and nine months, respectively, i. e. after the stumps were thoroughly healed, the number of deaths for calculation is 7. In 4 of the cases in which death occurred the survival periods were, respectively, two, four, five and six days, and in the 3 others two, three and six weeks. Only 1 death is admitted as due directly to the operation or to an unsatisfactory condition of the wound. This death (case 3) occurred in the earliest stage of inexperience and could presumably have been avoided with the advantage of later knowledge. The other deaths were attributable to medical complications or to septicemia or other fatal conditions antedating the operation. Inclusion of the entire 7 deaths occurring within six weeks or less after amputation gives a gross mortality rate of 15.5 per cent among the 45 patients or 12.3 per cent for the 57 major amputations. These figures based on an entirely unselected series represent a great statistical improvement over results previously obtained with patients in extremely poor average condition admitted to this public hospital.

Various details may be further analyzed as follows: With the aid of refrigeration it proved feasible to avoid amputation through the upper part of the thigh throughout the series. Among the 57 amputations in connection with which refrigeration was used, 21 were through the leg and 36 through the lower part of the thigh. With the amputations through the lower part of the thigh there were 4 deaths (mortality rate 11 per cent) and no failures of healing. With the amputations through the leg there were 3 deaths besides 5 failures of healing. Inasmuch as the deaths in general are not considered due to the operations, these figures are not a criterion of the relative safety of the two sites. Obviously, failure of healing is more likely at the lower site. However, successful healing was obtained in the leg in 13 cases, although in most or all of these the patients would have been candidates for higher operations without the refrigeration method. Also 1 death among the 8 reamputations contrasts with the prevalent idea of a high or prohibitive mortality rate and is evidence of the comparative safety of at

least trying the lower site when it is desired either to avoid constitutional strain or to preserve the knee joint.

COMMENT

Successful results require attention to technical details. Some of these are still undecided, but several can be mentioned provisionally as follows:

The tourniquet is a pure gum rubber tube, usually about 1 cm. in diameter. It is applied in two or, if necessary, three turns, one superimposed on the other to make the narrowest possible zone of compression. Unnecessary pain is caused by folds of the skin and can be largely prevented by care to avoid such folds and by preliminary chilling of the skin. Preliminary sedation is useful for nervous or apprehensive patients but is not needed for others. The eyes are covered, or a screen is interposed so that the patient does not see the operative field; stopping his ears with cotton prevents him from hearing the saw.

The tightness of constriction necessary to stop circulation differs with the patient, the location on the limb and other variables. Difficulties seem to be less in the thigh, in spite of its thickness, than in the upper part of the calf, where the main artery is protected between bones. Success may be had with a tourniquet above the knee or below the tubercle of the tibia but probably never between these levels. A little dark blood may accumulate as the result of inflow through the vessels of the marrow, especially of the tibia. It is prudent to inspect the limb one or more times twenty or thirty minutes after beginning refrigeration. Blanching of the foot is the rule, especially if the leg was elevated before applying the tourniquet. If any sizable arteries remain open the foot will be darkly cyanosed, and some error in the tourniquet should then be corrected. Any influx of blood makes for incompleteness or delay of anesthesia.

The optimum extent of preparatory refrigeration is undecided and is partly a matter of personal choice. Our experience with thin, weak patients with arteriosclerosis has definitely determined the time as follows: for the thigh, two and one-half hours; for disarticulation at the knee or through the middle of the leg, two hours; for the lower half of the leg or the foot, one and one-half hours; for the metatarsus or the toes, one hour. If the tourniquet is properly applied and securely fastened and the chilling is continuous to all parts at the correct temperature, there is complete local anesthesia so that the patient is not aware when the nerve is cut or the bone sawed.^{2a} Likewise there is no certainty whether the tourniquet should be prudently placed close to the

2a. Crossman, L. W.; Ruggiero, W. F.; Hurley, V., and Allen, F. M.: Ice Water Anesthesia for Leg Amputations, *J. Internat. Cong. Anesthetists*, to be published.

site of amputation, so as to leave the narrowest possible zone of chilled and bloodless tissue, or whether it may be fearlessly placed high, for example above the knee for amputation through the calf. It can only be said that no harm has been demonstrated thus far from either duration or extent of refrigeration. Marks resulting from the tourniquet have been visible for a day or two but have not proved significant. Contracture or paralysis has not resulted. More important, there has been no sign of thrombosis or other damage to blood vessels, and no special tendency to necrosis or infection indicating lowered resistance of tissues. The experience is not extensive enough to prove that such injuries will never occur, and for this reason positive rules are not yet formulated. Inasmuch as temperatures slightly above freezing have permitted animals' legs to survive more than two days without circulation,³ and rats' tails, four days or more,⁴ there seems theoretically to be little danger even to diseased limbs from the comparatively short periods of refrigeration employed clinically.

Obviously, everything warm should be kept away from the tissues during operations. Iced solution of sodium chloride has been used in connection with sawing and for other purposes. The object in view is not merely anesthesia of nerves but also anesthesia of protoplasm in order to prevent shock and injury to the vitality of the tissue. Possible adjuvant devices, such as keeping the limb on a bed of ice bags or a cold atmosphere for the operating room, have not appeared necessary for short operations but may be advisable for plastic and other long procedures.

As usual, undermining and dissection of tissues are avoided as far as possible. For amputations either through the calf or through the lower part of the thigh we have used modifications of the procedures devised by Dr. A. G. Fuller and introduced to City Hospital by Dr. F. W. Bancroft.⁵ Allowing rather liberal pads of soft tissue has seemed

3. Allen, F. M.: *Surgical Considerations of Temperature in Ligated Limbs*, *Am. J. Surg.* **45**:459, 1939; *Resistance of Peripheral Tissues to Asphyxia at Various Temperatures*, *Surg., Gynec. & Obst.* **67**:746, 1938; *Ligation and Refrigeration of Intestine*, *Surgery* **3**:893, 1938; *Physical and Toxic Factors in Shock*, *Arch. Surg.* **38**:155 (Jan.) 1939; footnote 1a.

4. Brooks, B., and Duncan, G. W.: *The Effects of Temperature on the Survival of Anemic Tissue*, *Ann. Surg.* **112**:130, 1940.

5. Low Thigh Amputation: With the Ruggiero modification a circular incision is made at the level of the lower border of the patella. All soft tissues are divided at this level, the knife traverses the knee joint, and the leg is removed. By dropping the end of the table the operator now faces the stump. The patella is turned up and dissected from its capsule. The soft tissues are freed anteriorly from the femur and on both sides. Posteriorly the shaft is bared, leaving undisturbed the attachments of the gastrocnemius, popliteus and plantaris muscles. The shaft of the femur is now divided about 2 inches (5 cm.) above the condyles. The main vessels are ligated, and the tourniquet is released. Bleeding points are

advisable, especially in the lower leg. Tightness is certainly to be avoided. Possibly because of the shrinking action of cold, primary union has apparently been favored in the danger zones by flaps which would ordinarily be considered as somewhat redundant.

The usual dressing after amputations has consisted of one layer of petrolatum gauze across the wound, then a few layers of dry gauze, surrounded by bare ice bags, for example one bag beneath and two sloping tentlike bags at the sides to avoid pressure on the limb. Often the desired skin temperature has been set arbitrarily at 15 C. (59 F.) for the first day after operation and has been raised gradually during the following days or even weeks. Until controllable apparatus is available, one method for gradually raising the temperature is to make the dressings a little thicker day by day. Both the degree and the duration of cooling are thus far entirely empiric and guided by the appearance of the wound. Sutures must be left in for an unusually long time. Healing is slowed in proportion as the temperature is kept reduced; therefore the temperature is raised as rapidly as conditions permit. In the experience to date, failures appear to have been chiefly due to mistaken judgment or inadequate regulation of postoperative temperature.

A number of broad questions of principle arise, of which only two will be mentioned briefly.

The optimum level of amputation is undecided, and there is uncertainty how far it may be changed by refrigeration. The work was begun¹ with a theoretic preference for low levels because of delayed shock and the strain of healing large wounds in weak patients and because of the better functional results which should be possible with proper prosthetic aids when the knee joint is preserved. Furthermore, deep postoperative chilling is more efficient in the leg than in the thigh. Therefore, the work has often contravened accepted rules, at least for experimental purposes. Operations have been performed at forbidden levels; areas of known infection have been cut across and then closed tightly or with only small drains. Granting that infectious organisms

ligated, and the deep fascia is closed transversely by interrupted sutures. The skin is closed in a similar manner. A moderate-sized dressing is applied, and the stump is placed on a posterior molded plaster splint.

Leg Amputation: The preferred site is the midleg, just below the bellies of the gastrocnemius muscle. A circular incision of the soft tissues is combined with a vertical incision over the lateral border of the fibula so that this bone may be removed at a level 3 inches (7.6 cm.) above the circular incision without extensive dissection. For convenience the fibula is first divided at the level of the circular incision and again 3 inches (7.6 cm.) higher. The tibia is now approached along the interosseous membrane and divided 2 inches (5 cm.) above the circular incision. The sharp anterior border is thoroughly beveled off. Closure is made by interrupted sutures in the deep fascia and in the skin. Silk technic is routine for sutures and ligatures.

are invisibly present in such legs up to the groin, a reason may be found for occasional mild or brief febrile attacks, and the question may be raised whether these are more debilitating or dangerous than a higher amputation. Excepting case 3, which represents mistakes of management in the pioneer period, the infectious dangers have largely been overcome with refrigeration. Even the sloughing of flaps after unduly low amputations has been confined to a narrow zone, entailing no important systemic disturbances and permitting of easy reamputation.

Misgivings have existed whether unduly severe or prolonged chilling may reduce local vitality, weaken physiologic barriers to diffusion so as to facilitate the penetration of bacteria or their products into the general circulation or create dangers of thrombosis or embolism. The extensive use of cold in another manner by Fay and a recent striking observation by McElvenny⁶ tend to oppose these suppositions. In the present series every death has had a rational explanation in an existing complication. Even if immediate operative shock is entirely prevented, some deaths may still be induced in enfeebled patients by delayed shock and the general strain of wound healing. The remarkably good preservation of general strength, the practical absence of postoperative pain or need for sedatives, the retention of appetite and spirits, the limitation of necrosis or infection even under unfavorable conditions and the total absence of thrombosis or embolism all testify to the lack of injury from either the reduced temperature or the tourniquet and establish the life-saving value of the new method in the surgical treatment of peripheral vascular disease.

SUMMARY

The experience in a series of 45 cases has convinced us of the value of the refrigeration method for amputations. Further improvements may be hoped for with the gaining of more knowledge of optimum postoperative temperatures and the introduction of apparatus for maintaining such temperatures. It is believed that the principle will find wider uses, and at the present time its adoption for emergency and military operations is particularly to be emphasized.

6. McElvenny, R. T.: The Effect of Cooling Traumatized and Potentially Infected Limbs, *Surg., Gynec. & Obst.* 73:263, 1941.

LYMPHOSARCOMA OF THE RECTUM

JOSEPH A. TUTA, M.D., PH.D.

AND

PETER A. ROSI, M.D.

CHICAGO

Lymphosarcoma of the rectum is rarely recognized as such before histologic study of the tissue has been made. In 1929, Rankin and Chumley¹ reported a series of 18 cases of lymphosarcoma of the colon and the rectum. The location of the tumors was as follows: Thirteen were in the cecum; one was in the descending colon; one was in the sigmoid; and three were in the rectum. In 1933, Smith² found 17 recorded instances of lymphosarcoma of the rectum and the sigmoid and added the cases of 6 patients who had been treated at the Mayo Clinic since 1926. Raiford³ reviewed a series of 45 cases of lymphoid tumor of the gastrointestinal tract from the Johns Hopkins Hospital. The distribution was as follows: In 13 the tumor was in the stomach; in 1, in the duodenum; in 19, in the ileum; in 11, in the colon, and in 1, in the rectum. Lynch and Hamilton⁴ recently reported 3 more cases. Pattison⁵ in reporting a series of 6 cases of malignant lymphoma of the gastrointestinal tract described 1 tumor involving the rectum.

According to Rankin and Chumley, the clinical diagnosis of lymphosarcoma of the rectum is rarely suspected before operation since there are no characteristic features which might be used to distinguish it from the tumors more commonly found in this region. These tumors predominantly affect men. Sutton⁶ stated that the growths are apt to be

From the Grant Hospital, the Department of Pathology, the University of Illinois College of Medicine and the Department of Surgery, Northwestern University Medical School.

1. Rankin, F. W., and Chumley, C. L.: Lymphosarcoma of the Colon and Rectum, *Minnesota Med.* **12**:247-253 (May) 1929.

2. Smith, N. D.: Lymphosarcoma of the Rectum and Sigmoid, *Proc. Staff Meet., Mayo Clin.* **8**:437-438 (July 19) 1933.

3. Raiford, T. S.: Lymphoblastomas of the Gastrointestinal Tract, *Arch. Surg.* **26**:813-835 (May) 1933.

4. Lynch, J. M., and Hamilton, G. J.: Lymphosarcoma of the Rectum, *Tr. Am. Proctol. Soc.* **40**:221-226, 1939.

5. Pattison, A. C.: Malignant Lymphoma of the Gastrointestinal Tract, *Arch. Surg.* **29**:907-922 (Dec.) 1934.

6. Sutton, C. J.: Primary Lymphosarcoma of the Rectum, *Canad. M. A. J.* **26**:71-73 (Jan.) 1932.

located in the lower portion of the rectum. The inguinal nodes may be involved.

Grossly, tumors diagnosed as lymphosarcoma are divided into the polypoid and the diffuse infiltrative type. The polypoid formations are firmer in consistency than the softer adenomatous polyps. The surfaces made by sectioning the gross specimen often have a homogeneous pale gray surface resembling brain tissue which has been fixed in solution of formaldehyde. The process extends along the submucosa and at first forms a localized submucosal thickening which by pressure may cause necrosis or which may invade the mucosa. Later, ulceration and bleeding may follow. In some instances the mucosa may move freely over the tumor mass. The tunica muscularis is invaded and replaced by lymphoid tissue. In many of the reported cases the infiltration does not extend beyond the serosa. Lynch and Hamilton noted that the lines of cleavage are more easily demarcated than those one usually encounters with carcinoma. In a case described by Martin,⁷ the rectal valves had a thickened appearance, and there were several adjacent ulcerated areas, but the process did not grossly give the impression of being malignant.

REPORT OF A CASE

A man 27 years of age was admitted to the Grant Hospital complaining of a mass which protruded at times from the anus. He had noticed also some bleeding from the anal region, which he attributed to hemorrhoids. There was no history of injection treatments for hemorrhoids. A roentgen chest plate showed nothing abnormal. Roentgen studies of the colon revealed no abnormalities. A proctoscopic examination was made, and a polypoid mass was noted in the right posterior quadrant of the anus about 0.5 cm. above the pectinate line. One pea-sized polyp was fulgurated near the rectosigmoid junction. No biopsy was made. The remaining mucosa was normal. The polypoid tumor mass was excised by removing the skin distal to it and removing about 1 cm. of mucosa around the tumor. The mucosa was dissected from the external and internal sphincters and the hemorrhoids removed. The lobulated sessile tumor mass measured 2.3 by 1.5 by 1.0 cm. The cut surface was homogeneous pale gray and firm.

Microscopic Description.—There were large areas of lymphoid cells surrounded by varying amounts of connective tissue. The infiltrations involved the submucosa, the tunica muscularis and the subserosa. In some places the mucosa was invaded by lymphoid cells, and in others the main tumor mass caused atrophy of the mucosa by pressure. The type cell was slightly larger than a lymphocyte. There were a few larger cells with a moderate amount of cytoplasm. In the centers of some of the larger lymphoid areas, the cells were less closely packed than at the periphery, and there were a few larger lymphoid cells measuring twice the diameter of the predominant cell. These large lymphoid islands resem-

7. Martin, W. C.: Lymphoblastoma of the Gastrointestinal Tract, Am. J. Roentgenol. **36**:881-891 (Dec.) 1936.

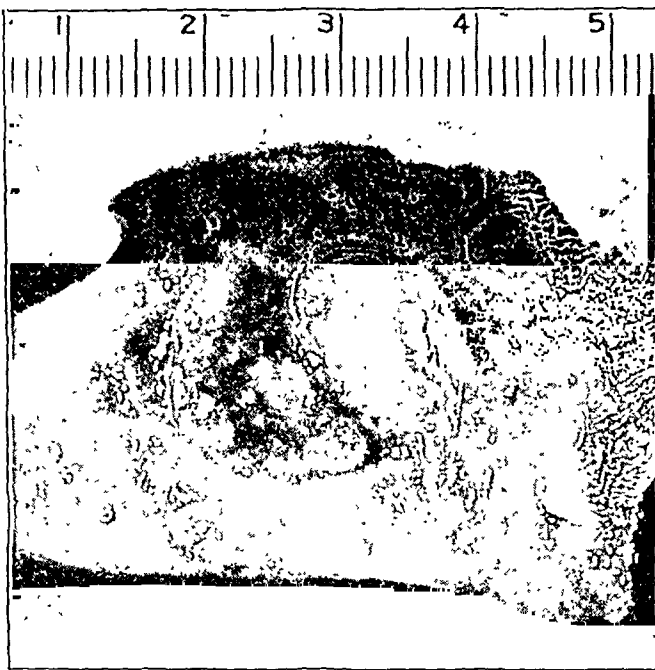


Fig. 1.—Polypoid tumor mass, measuring 2.3 by 1.5 by 1.0 cm., which was located just above the anal margin.

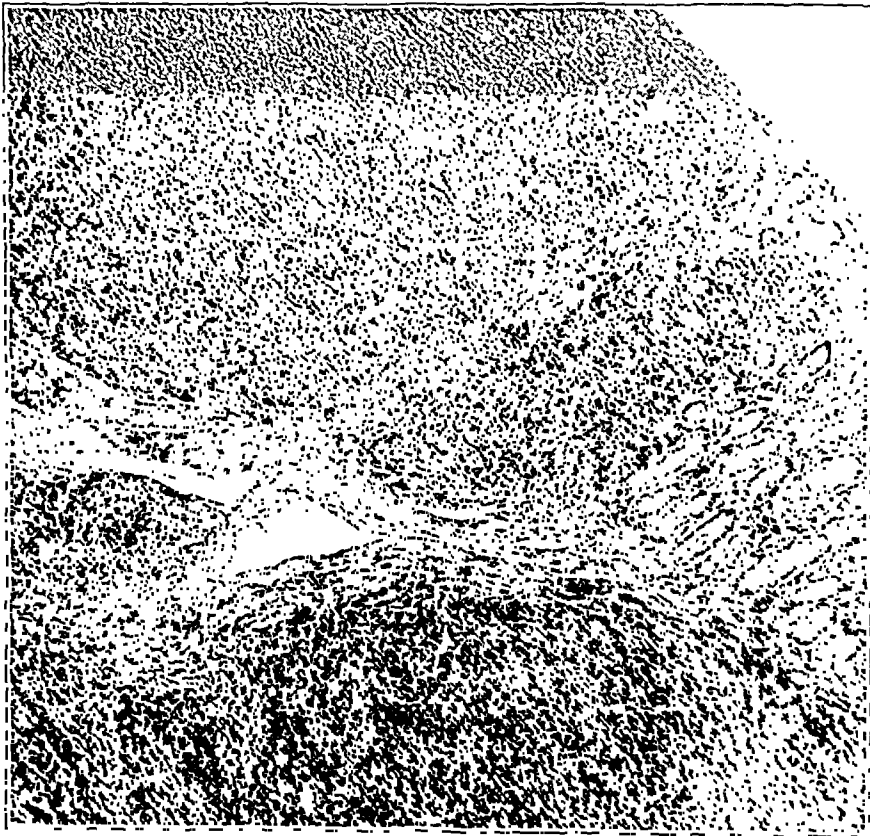


Fig. 2.—Photomicrograph ($\times 40$) showing the large islands of lymphoid tissue surrounded by various amounts of connective tissue. These structures extended from the mucosa to the serosa.

bled somewhat a giant follicle, but there was no definite cortical layer of delimiting cells, and the large lymphoid areas fused in many places. There were a few small foci of inflammatory cells, including plasma cells, eosinophils and polymorphonuclear leukocytes. These were located in the compressed submucosa, which was not invaded by lymphoid cells. There were also some pigment-laden macrophages in the submucosa. The Perdrau silver stain for reticulum fibers showed large areas with only a few reticulum fibers. A few areas showed numerous reticulum fibers.



Fig. 3.—Photomicrograph showing under higher magnification ($\times 112$) the diffuse lymphoid infiltrations which extended into the mucosa, causing ulceration and bleeding.

COMMENT

According to Ewing,⁸ there are two general types of lymphosarcoma arising in lymphoid tissue. They are the large round cell lymphosarcoma or reticulum cell sarcoma and the small round cell sarcoma or malignant lymphocytoma. The tumor described in this paper falls under the latter

8. Ewing, J.: *Neoplastic Diseases*, ed. 4, Philadelphia, W. B. Saunders Company, 1940, p. 424.

classification. Symmers⁹ objected to the term "reticulum cell lymphosarcoma" and suggested that the more appropriate term is "large round cell sarcoma." Krumbhaar¹⁰ stated that the lymphocytic type is more radiosensitive than the reticulum cell type, and according to Raiford the small cell type is the less malignant. Many of the lymphoid tumors of the lymph nodes and of the gastrointestinal tract do not easily fall under a definite classification, and it has been customary for many investigators to group them under the general head of malignant lymphoma or lymphoblastoma. These include Hodgkin's disease, lymphosarcoma of the lymphocytic type, reticulum cell sarcoma, multiple giant follicular lymphadenoma (follicular lymphoblastoma) and others. Mayer and Thomas,¹¹ quoting Baehr and Rosenthal,¹² stated that lymphoma of the giant follicular type has not been found in the gastrointestinal tract.

Before a diagnosis of relatively early lymphosarcoma of the rectum can be definitely established, chronic inflammatory process and benign lymphoid tumor must be ruled out. Particularly in lymphoid tissue, the transition between simple inflammatory hyperplasia, such as may be seen in tuberculosis, and benign neoplasm of lymphoid character may be difficult to distinguish. Likewise, the transformation from benign to malignant tumor can present similar obstacles in establishing a definite diagnosis. In the gastrointestinal tract especially, according to Ewing,¹³ lymphoid tumor may closely resemble infectious granuloma, owing to superimposed chronic inflammatory infiltrations. The tumor reported had a predominantly lymphoid structure with only slight inflammatory foci.

Although the patient gave no history of having had injections for hemorrhoids, the possibility of a rectal tumor of chemical origin was considered, particularly because of the location of the mass just above the dentate margin. Jackman¹⁴ recently described the histologic features of tumors caused by injections of oil, viz., vacuolation and foreign body

9. Symmers, D.: Giant Follicular Lymphadenopathy With or Without Splenomegaly, *Arch. Path.* **26**:603-647 (Sept.) 1938.

10. Krumbhaar, E. B.: The Lymphomatoid Diseases (the So-Called Lymphoblastomas), *J. A. M. A.* **106**:286-291 (Jan. 25) 1936.

11. Mayer, S., Jr., and Thomas, H. M., Jr.: Follicular Lymphoblastoma, *Bull. Johns Hopkins Hosp.* **64**:315-338 (May) 1939.

12. Baehr, G., and Rosenthal, N.: Malignant Lymph Follicle Hyperplasia of Spleen and Lymph Nodes, *Am. J. Path.* **3**:550, 1927.

13. Ewing, J.: General Pathology of Lymphosarcoma, *Bull. New York Acad. Med.* **15**:92-103 (Feb.) 1939.

14. Jackman, R. J.: The Differential Diagnosis, Pathologic Aspects and Treatment of Rectal Tumors of Chemical Origin: Report of Cases, *Proc. Staff Meet., Mayo Clin.* **15**:188-192 (March 20) 1940.

giant cells; neither of these was present in the lymphoid tumor described in this paper. Moreover, the circumscribed character of the polypoid mass, the age of the patient, the location of the mass without signs of adjacent inflammatory changes and the absence of symptoms of tuberculosis, syphilis, fissures, fistulas or trauma together with the insidious onset and the histologic characteristics of neoplastic growth give a composite picture which is incompatible with simple inflammatory hyperplasia.

Since the tumor was fairly well circumscribed and there was no evidence of metastases or invasion beyond the serosa, the possibility of benign lymphoma was considered. In the literature one sees records of cases of borderline lymphoid tumors in which there was difficulty in deciding from histologic studies whether the given tumor was benign, malignant or simply inflammatory. Hayes, Burr and Pruitt¹⁵ recently emphasized the limitations which must necessarily be placed on the histologic interpretation of certain lymphoid tumors of the colon and the rectum. They found 20 cases classified in the literature as cases of benign lymphoma. Dukes¹⁶ described 3 instances of benign lymphoid tumor of the rectum and stated that the structure of the tumors consisted of groups of lymph follicles lying in the submucosa and covered by mucous membrane. Two of the patients showed no evidence of recurrence after five years.

In the case that we have described there was definite histologic evidence that we were dealing with a malignant tumor. Of particular importance was the fact that no definite lymph follicle formations, such as may be seen in cases of simple lymphoma, could be found. The large islands of lymphoid cells did not resemble the giant follicles seen in certain forms of lymphoma involving the lymph nodes and the spleen. No analogy can be drawn between the structure of the tumor under discussion and the rare condition described by Ewing¹³ as systemic pseudoleukemia; the latter is characterized by many small lymphomas in the mucosa of the gastrointestinal tract, and histologic study shows many well formed lymph follicles. The lack of follicular structure and the fusion of the lymphoid islands indicated a diffuse process. Besides, not only the submucosa was involved but the entire wall from the ulcerated mucosa to the serosa.

Since the histologic structure of the tumor indicated that it was of the less malignant type, the early wide excision of the primary growth may serve to cure the patient. At the time of writing, seven months after the operation, there has been no recurrence, but a guarded

15. Hayes, H. T.; Burr, H. B., and Pruitt, L. T.: Lymphoid Tumors of the Colon and Rectum, *Surgery* **7**:540-545 (April) 1940.

16. Dukes, C.: Lymphoma of the Rectum, with Report of Three Cases, *Proc. Roy. Soc. Med.* **27**:926-927, 1934.

prognosis must be made in view of the possible lymphoid involvement of other segments of the gastrointestinal tract which may occur years later.

SUMMARY

Lymphoid tumor of the rectum and colon presents an interesting problem in surgery and tumor pathology. The difficulties in the histologic interpretation of lymphoid tumor of the gastrointestinal tract are emphasized. A biopsy of polyps of the rectum and colon and especially of growths near the anorectal region is indicated. The treatment consists of local wide resection of the tumor mass followed by irradiation of the region.

CYSTIC TUMOR OF THE TONGUE

REPORT OF AN UNUSUAL CASE

GEORGE W. DUNCAN, M.D.

AND

R. A. DANIEL JR., M.D.

NASHVILLE, TENN.

The literature contains but few reports of cysts and cystic tumors of the tongue, regardless of type. One would expect these lesions to be encountered more frequently when the numerous glands and the complex embryologic development of this organ are considered.

Cyst formation may result from incomplete obliteration of the lingual portion of the thyroglossal duct. This structure is present in embryos 4 weeks of age (2.5 mm. stage) and normally atrophies during the sixth week of fetal life.¹ Cystic tumors of the tongue are usually situated in the midline beneath the foramen caecum. They are lined by stratified squamous epithelium or by ciliated epithelium.²

Mucous or retention cysts result when mucous glands at the base of the tongue become obstructed, with subsequent accumulation of secretion. They have been described most often in infants and may become large enough to produce stridor and asphyxia. They are located between the epiglottis and the foramen caecum and may be either in the midline or laterally placed.³ In Scheier's⁴ case the pharyngeal wall was involved. Retention cysts of Blandin and Nuhn's glands have been reported but are extremely rare.⁵

Wenglowksi⁶ examined a large number of embryos and cadavers and found numerous small cysts at the base of the tongue. He expressed the belief that these were vestiges of the primitive lingual duct. In the fourth month of embryonic life this duct is broad and branched; small

From the Department of Surgery, Vanderbilt University.

1. Arey, L. B.: *Developmental Anatomy*, Philadelphia, W. B. Saunders Company, 1938.

2. Clute, H. M., and Cattell, R. B.: *Ann. Surg.* **92**:57-66, 1930.

3. Post, H.: *Ztschr. f. Kinderh.* **46**:566-568, 1928. Thomas, E.: *ibid.* **47**:168, 1929. Vollmer, H.: *Klin. Wchnschr.* **1**:1212, 1922. Forsyth, E. A.: *Laryngoscope* **21**:1145-1150, 1911.

4. Scheier, M.: *Berl. klin. Wchnschr.* **51**:330, 1914.

5. (a) Butlin, H. T., and Spencer, W. G.: *Diseases of the Tongue*, London, Cassel & Company, 1900. (b) Fitzwilliams, D. C. L.: *The Tongue and Its Diseases*, New York, Oxford University Press, 1927. (c) Curtis, B. F.: *Ann. Surg.* **27**:662, 1898.

6. (a) Wenglowksi, R.: *Arch. f. klin. Chir.* **98**:150, 1912. (b) Colp, R.: *Surg., Gynec. & Obst.* **40**:183-195, 1925.

portions may become disconnected and form isolated cysts. These cysts have been incorrectly considered dermoids by some authors. Microscopic examination reveals a lining of stratified squamous or ciliated epithelium. The absence of skin appendages differentiates them from true dermoids.

In 1906 Nicoll and Teacher⁷ reported a cystic teratoma of the tongue containing derivatives of all three germ layers. Numerous reports of dermoid cysts⁸ of the congenital inclusion type involving the floor of the mouth have been published, but no similar cysts occurring in the numerous fusion lines of the tongue have been reported.

Lymphangioma and hemiangioma are occasionally encountered and may involve any portion of the tongue.⁹

In this publication we wish to present the clinical and pathologic features of an unusual tumor of the tongue and to consider also its embryologic aspects.

REPORT OF A CASE

C. W., a Negro boy 2 months old, was admitted to the Vanderbilt University Hospital on Sept. 7, 1939. Shortly after birth he was observed to have an abnormally large tongue. This enlargement progressively increased, and the substitution of feeding by a bottle with a nipple having a large orifice became necessary. The rate of growth was most rapid during the week prior to admission. At the time of admission examination of the child revealed a large tumor in the body of the tongue (fig. 1), displacing the organ upward into the roof of the mouth. The tumor was round and had a faintly bluish hue, visible through the mucous membrane on the dorsal and ventral surfaces of the tongue. In situ it measured about 2.5 cm. in diameter. The tumor was tense, fluctuant and well circumscribed and was easily transilluminated. Preoperative examination revealed a normal sulcus terminalis and a shallow foramen caecum. The papillae and the lingual tonsils also appeared normal.

Operation was performed on September 9 with the patient under ether anesthesia. The tongue was retracted upward by a suture taken through its tip. Incision was made through the mucous membrane covering the ventral surface, and the tumor was dissected free from the surrounding lingual muscle. The muscle was closed with fine interrupted catgut sutures and the mucous membrane with interrupted silk sutures. The wound healed rapidly, and the tongue has since assumed a normal contour.

Gross Appearance of the Tumor.—The tumor measured 2.9 cm. in diameter. The outer surface was smooth. Its consistency was firm but definitely cystic. On incision the cyst was found to be filled with viscid cloudy fluid. The wall measured 2 to 3 mm. in thickness. The inner surface also was smooth in appearance, but on magnification ($\times 30$) small round projections were visible in some areas, while in others there was no elevation or depression.

Microscopic Appearance.—The histologic structure of the cyst was complex (fig. 2). An epithelial lining was present throughout. Stratified squamous

7. Nicoll, J. H., and Teacher, J. H.: Glasgow M. J. **66**:216-222, 1906.

8. New, G. B., and Erich, J. B.: Surg., Gynec. & Obst. **65**:48-55, 1937. Fitzwilliams.^{5b} Curtis.^{5c} Wenglowski.^{6a} Colp.^{6b} Nicoll and Teacher.⁷

9. Funk, E. H.: Cavernous Angioma of Tongue, J. A. M. A. **79**:1113-1115 (Sept. 30) 1922. Arrowsmith, H.: Laryngoscope **25**:94, 1915. Tardieu, A., and Dechaume, M.: Rev. de chir., Paris **70**:142-148, 1932. Baumgartner, H.: Schweiz. med. Wchnschr. **55**:1030-1033, 1925. Curtis.^{5c} Wenglowski.^{6a}

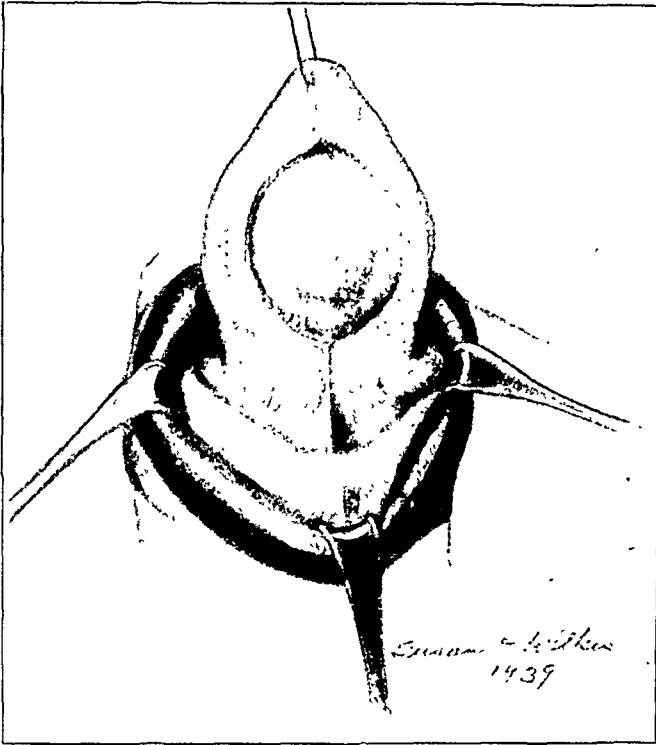


Fig. 1.—Ventral surface of the tongue after the dissection of the mucous membrane from the surface of the tumor.

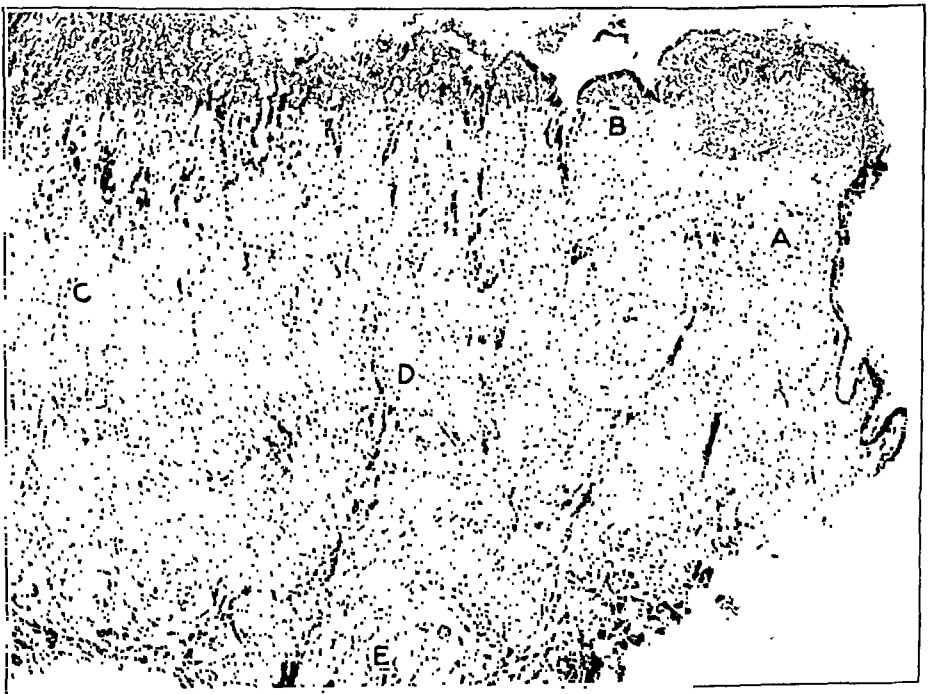


Fig. 2.—Photomicrograph showing the complex histologic pattern of the wall of the tumor: *A*, stratified squamous epithelium; *B*, simple columnar epithelium; *C*, portion containing glands similar to those found in the fundus of the stomach; *D*, smooth muscle; *E*, striated muscle of the tongue.

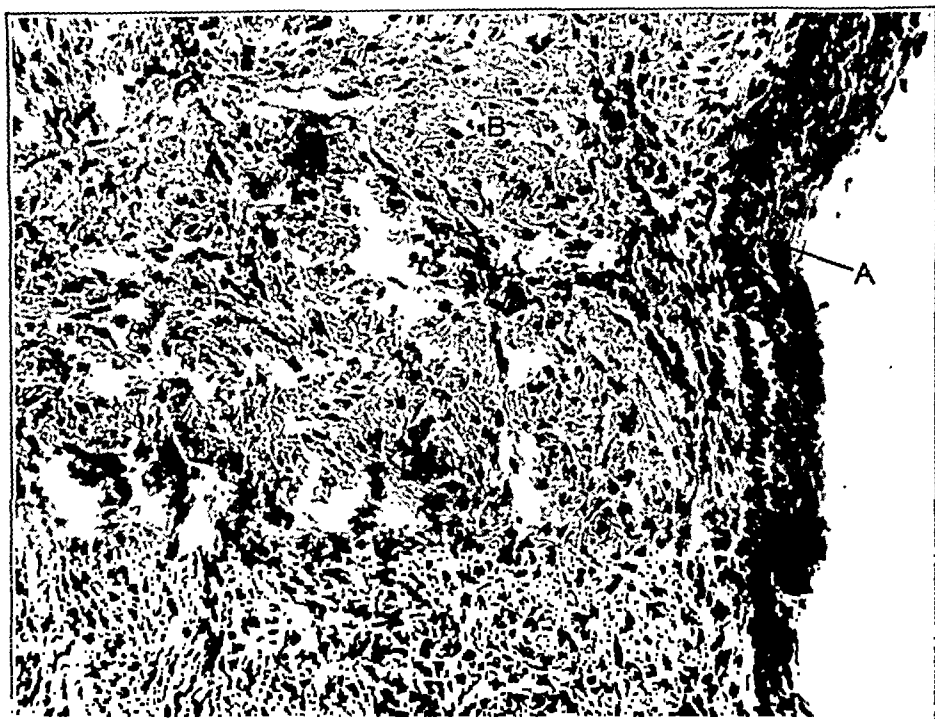


Fig. 3.—Photomicrograph showing the lining of stratified squamous epithelium and the smooth muscle in the wall of the tumor.



Fig. 4.—Photomicrograph showing higher magnification of a portion of the cyst wall containing (A) glands and (B) muscular layers similar to those of the fundus of the stomach.

epithelium was seen in some areas, which had the appearance of that normally lining the mouth (figs. 2 and 3). No cornification or skin appendages were present. Other areas were lined by simple columnar epithelium of varying height (fig. 3). Still other areas were lined with mucous membrane similar to that seen in the fundus of the stomach, viz., simple columnar epithelium, with glands showing chief cells, mucous neck cells and parietal cells (fig. 4). The muscularis mucosae and the oblique, circular and longitudinal layers of smooth muscle were demonstrable in this portion. Smooth muscle was present in the entire wall, but the arrangement was much less definite in portions not containing glands and lined by stratified squamous epithelium and simple columnar epithelium. The outermost smooth muscle fibers of the wall interlaced with the striated muscle of the tongue.

COMMENT

Since the tumor described obviously originated early in embryonic life, a brief review of the embryology of the tongue and other related tissues found in the tumor may be helpful in understanding its origin and structure.

The tongue has been described¹ as being primarily of pharyngeal derivation, its forward growth into the mouth being secondary. It consists of two distinct portions, the body or apical portion and the root or posterior portion. These represent different primordia in the embryo and are separated in the adult tongue by the sulcus terminalis. The body or apical portion originates in front of the second branchial arches; the root develops primarily from the second branchial arches but receives contributions also from the third and the fourth. Examination of the pharyngeal floor in the fifth week (5 mm. stage) of embryonic life reveals an unpaired swelling between the first pair of pouches, the tuberculum impar. It was believed by His that the growth of this tubercle formed the body of the tongue. In 1869 Dursy, and later Hammar and other authors, described the organ as having a paired origin.¹⁰ It is now generally accepted that the tuberculum impar lags in development and takes little or no part in the subsequent development of the tongue. The paired lateral lingual swellings formed by the first branchial arches also are visible at the fifth week. Simultaneous with the appearance of these three primordia, the root of the tongue is represented by a medial ventral elevation of the copula which develops by the fusion of the two second branchial arches. The lateral lingual swellings grow rapidly, joining at the median septum and forming the body of the tongue. The copula with the adjacent portions of the second arches increases in size to form the root of the tongue. These fusions are well advanced during the sixth week and are completed soon afterward. The tongue is later encroached on by the third and fourth arches, and there is a general forward dislocation of the mucous membrane. During the

10. Keibel, F., and Mall, F. P.: *Human Embryology*, Philadelphia, J. B. Lippincott Company, 1912.

seventh week the organ becomes elevated and assumes prominence through the internal development of striated muscle. This muscle belongs ancestrally to the region caudad to the branchial arches, but there seems to be no definite proof that the muscles of the tongue do not arise from the mesoderm of the floor of the mouth.

During the early development of the tongue other related tissues represented in this tumor have begun their development. In the third week of embryonic life the embryonic disk begins to fold into a cylindric mass and carries the endoderm with it into the head region, forming a blind tube, the foregut. This blind tube comes in contact with the ectoderm by the formation of the pharyngeal membrane which separates the foregut from the stomadeum. This membrane ruptures at the beginning of the fifth week of embryonic life, simultaneously with the appearance of the primordia of the tongue. The presence of a fetal cell rest in the floor of the pharynx at the time of appearance of the anlage of the tongue would make possible its inclusion and forward displacement by subsequent growth of the lateral lingual swellings. Forward displacement might also be produced by the anterior migration of the muscle of the tongue, assuming that the muscle arises from the region caudal to the pharynx.

SUMMARY

The clinical and pathologic features of an unusual tumor of the tongue are presented. The embryology of the tongue and of related tissues represented in the tumor is reviewed. The structure of this tumor suggested a cell rest representing more than one germ layer, originating probably between the third and fifth weeks of embryonic life. Its conclusion and forward displacement appear to be definitely related to the development of the tongue.

CORRECTION

In the article by Drs. J. K. Donaldson and E. B. Sive and Mr. Norman Lewis entitled "Intestinal Obstruction," in the November issue (*ARCH. SURG.* **43**:811, 1941), the first word in the third sentence from the bottom of page 827 should read "Nine" instead of "No."

In the eighth line from the bottom of page 830, "July 1931" should read "July 1939."

COMBINED SURGICAL AND PHYSIOLOGIC TREATMENT OF CRYPTORCHIDISM

DESCRIPTION OF AN OPERATIVE PROCEDURE

ROBERT H. ABRAHAMSON, M.D.
NEW YORK

Maldescent of the testis is fairly common; the incidence ranges from 0.2 to 1.02 per cent of the adult male population.¹ Many theories have been evolved and propounded in an effort to explain the causation of this abnormality. These have been summarized and analyzed by several authors.²

Many operative procedures for the correction of cryptorchidism have been described. All consist in: (1) lengthening those structures attached to the testis, such as the vas deferens and the blood vessels, so that the testis can be placed in the scrotum and (2) retaining the testis in the scrotum after it has been brought down. Surgeons agree that the cord must be lengthened in order that the testis may be placed in the scrotum. However, there are several differences in the methods of retaining the testicle in the scrotum once it has been placed there.

The more commonly used methods of retaining the testis within the scrotum are: (1) narrowing the neck of the scrotum by sutures to prevent retraction of the testis; (2) suturing the testis to the scrotum; (3) drawing the testis by suture, wire or elastic, to some fixed point outside the scrotum; (4) transplanting the testis to the opposite scrotal sac, using the scrotal raphé to prevent retraction; (5) fixating the

From the Surgical Service of Dr. Milton Bodenheimer, Hospital for Joint Diseases.

1. (a) Bevan, A. D.: Operation for Undescended Testicle and Congenital Inguinal Hernia, *J. A. M. A.* **33**:773 (Sept. 23) 1899. (b) Goetsch, A.: Undescended Testis: Review of Thirty-Two Operative Cases, *Am. J. Surg.* **12**:63, 1931. (c) Love, A. G., and Davenport, C. B.: Defects Found in Drafted Men: Statistical Information Compiled from the Draft Records, Washington, D. C., Government Printing Office, 1920. (d) Marshall, H.: Contribution to Statistics of Hernia Among Recruits for the British and Conscripits for the French Army, *Edinburgh M. & S. J.* **50**:15, 1838. (e) Ziebert, K. A.: Ueber Kryptorchismus und seine Behandlung, Thesis, Heidelberg, 1898, Tübingen, H. Laupp, 1898.

2. (a) Burdick, C. G., and Coley, B. L.: Undescended Testicle, *Ann. Surg.* **84**:867, 1926. (b) Cabot, H., and Nesbit, R. M.: Undescended Testis, *Arch. Surg.* **22**:851 (May) 1931. (c) Guiteras, R.: Urology: The Diseases of the Urinary Tract in Men and Women, New York, D. Appleton and Company, 1912, vol. 2, p. 589. (d) Wangenstein, O. H.: The Undescended Testis, *Arch. Surg.* **14**:663 (March) 1927.

testis into the thigh; (6) multiple stage procedures, by which the testis is fixed temporarily to the posterior wall of the inguinal canal.

Orchidopexy for cryptorchidism was first reported by Rosenmerkel.³ Bevan^{1a} described a procedure in which the spermatic vessels are divided to allow the testis to enter the scrotum. Moschcowitz⁴ used a similar procedure. Ombrédanne⁵ brought the testis through the scrotal raphé so that both testes were in the same compartment of the scrotal sac. Cabot and Nesbit^{2b} reviewed the various methods of placing traction on the testis and added the use of elastic traction to lengthen the cord and retain the testis in the scrotum. Multiple stage procedures for abdominal cryptorchidism have been described and successfully used by Cabot,⁶ Keetley⁷ and later Torek⁸ suggested fixation of the testis into the thigh, and this procedure has been extensively used by several operators.⁹ Burdick and Coley¹⁰ have had the widest experience and achieved the most successful results with this method.

The importance of the endocrine biology of the testis was first brought into prominence by Sand¹¹ in 1918 by his experiments with cryptorchidism. The use of endocrine preparations in the treatment of undescended testes was instigated by the investigations of Zondek and Aschheim¹² and Evans and Simpson,¹³ who demonstrated the gonadotropic principle in the anterior lobe of the pituitary gland. Moore¹⁴

3. Rosenmerkel, J. F.: Ueber die Radicalcur des in der Weiche liegenden Testikels bei nicht vollendetem Descensus desselben, Munich, K. Lindauer, 1820.

4. Moschcowitz, A. V.: The Anatomy and Treatment of Undescended Testis, with Especial Reference to the Bevan Operation, *Ann. Surg.* **52**:821, 1910.

5. Ombrédanne, L.: L'orchidopexie chez l'enfant, *Gaz. méd. de France* **2**:118, 1928.

6. Cabot, H.: Treatment of Abdominal Cryptorchidism, *J. Mt. Sinai Hosp.* **4**:596, 1938.

7. Keetley, C. B.: Temporary Fixation of Testis to Thigh: A Series of Twenty-Five Cases Operated on for Undescended Testis, *Lancet* **2**:279, 1905.

8. Torek, F.: The Technique of Orchidopexy, *New York M. J.* **90**:948, 1909.

9. Meyer, H. W.: Undescended Testicle, *Surg., Gynec. & Obst.* **44**:53, 1927. Wangenstein, O. H.: The Surgery of the Undescended Testis, *ibid.* **54**:219, 1932. Cabot.⁶

10. Burdick, C. G., and Coley, B. L.: Undescended Testicle, *Ann. Surg.* **98**:495, 1933.

11. Sand, cited by Møller-Christensen, E.: Ueber Kryptorchismus und seine Behandlung mit Sexualhormonen, *Acta path. et microbiol. Scandinav.*, 1938, supp. 37, p. 391.

12. Zondek, B., and Aschheim, S.: Hypophysenvorderlappen und Ovarium: Beziehungen der endokrinen Drüsen zur Ovarialfunktion, *Arch. f. Gynäk.* **130**:1, 1927.

13. Evans, H. M., and Simpson, M. E.: Antagonism of Growth and Sex Hormones of the Anterior Hypophysis, *J. A. M. A.* **91**:1337 (Nov. 3) 1928.

14. Moore, C. R., and Price, D.: Some Effects of Fresh Pituitary Homoplasts and of the Gonad-Stimulating Substance from Human Pregnancy Urine on the Reproductive Tract of the Male Rat, *Am. J. Physiol.* **99**:197, 1931.

showed the action of chorionic gonadotropin on the reproductive tract of the male rat. Cole and Hart¹⁵ found a gonad-stimulating substance in the serum of pregnant mares which was effective in increasing the size of the testes of the rat, and Engle¹⁶ found that extracts of the anterior lobe of the pituitary gland were effective in causing descent of the testes in the prepubescent monkey.

Browne,¹⁷ along with several other investigators,¹⁸ expressed the opinion that endocrinotherapy for this condition is useless and even dangerous and warned of harmful results. Eisenstaedt,^{18c} in noting the degenerative and injurious effects of endocrine preparations on the undescended testis, expressed his belief that such treatment makes subsequent operative intervention more difficult. One result of his investigations which is of great importance is that comparatively enormous doses of chorionic gonadotropin administered to animals did not cause any ill effects in those animals in which the testis was in the normal position. In a recent article, Johnson¹⁹ expressed the belief that endocrinotherapy should be used only as adjunctive therapy in cases of oncoming puberty. From a careful review of 15 cases of cryptorchidism treated with chorionic gonadotropin (I personally followed many of the patients over a period of one year), Arnheim²⁰ concluded that failures with chorionic gonadotropin (follutein) are most often due to mechanical obstructions which require surgical intervention and that even in these cases such therapy is valuable.

Goldman²¹ used large doses of chorionic gonadotropin in a carefully studied group of 11 cases and had successful results in 10 cases. In a

15. Cole, H. H., and Hart, G. H.: The Potency of Blood Serum of Mares in Progressive Stages of Pregnancy in Effecting the Sexual Maturity of the Immature Rat, *Am. J. Physiol.* **93**:57, 1930.

16. Engle, E. T.: The Action of Extracts of Anterior Pituitary and of Pregnancy Urine on the Testes of Immature Rats and Monkeys, *Endocrinology* **16**:506, 1932.

17. Browne, D.: The Diagnosis of Undescended Testicle, *Brit. M. J.* **2**:168, 1938.

18. (a) Cabot, H.: Management of Patients with Retained Testes, *Radiol. Rev. & Mississippi Valley M. J.* **58**:198, 1936. (b) Cole, H. H.: On the Biological Properties of Mare Gonadotropic Hormone, *Am. J. Anat.* **59**:299, 1936. (c) Eisenstaedt, J. S.; Appel, M., and Fraenkel, M.: The Effect of Hormones on the Undescended Testis, *J. A. M. A.* **115**:200 (July 20) 1940. (d) Mimpriss, T. W.: The Treatment of Imperfect Descent of the Testes with Gonadotropic Hormones, *Lancet* **1**:497, 1937.

19. Johnson, W. W.: Cryptorchidism, *J. A. M. A.* **113**:25 (July 1) 1939.

20. Arnheim, R. E.: The Treatment of Undescended Testes with Gonadotropic Hormones, *J. Mt. Sinai Hosp.* **4**:1036, 1938.

21. Goldman, A.; Stern, A., and Lapin, J.: The Treatment of Undescended Testes by the Anterior Pituitary-Like Principle from the Urine of Pregnancy, *New York State J. Med.* **36**:15, 1936.

review of 117 cases of cryptorchidism, Fèvre and Eck²² stated that they used chorionic gonadotropin and testosterone propionate successfully in the treatment of this condition. They expressed their opinion that up to puberty endocrinotherapy should be used and that then, if necessary, operation should be performed. They used the transscrotal procedures suggested by Ombrédanne.⁵ In an extensive review of the problem of undescended testis, Thompson and Heckel²³ commented that it is important to maintain an open mind about endocrinotherapy, although they stated their belief that many of the reports have been overenthusiastic.

It is not my purpose, nor is it within the scope of this report, to review the entire results of endocrinotherapy on the descent of the testis or to enter into the controversy on this subject. Suffice it to say that since the aforementioned experimental scientific contributions were made, many investigators and clinicians have attempted to influence the course of cryptorchidism by the use of several endocrine preparations with varied and controverted results.²⁴

With varying degrees of success, several different endocrine preparations have been used in an attempt to effect the descent of the testis to the normal position. Those credited with the greatest success are: thyroid, gonadotropic substance recovered from the urine of pregnant women, gonadotropic substance recovered from placental tissue, gonadotropic substance recovered from the serum of pregnant mares, desiccated pituitary gland substance (given orally), extracts of the anterior lobe of the pituitary gland and testosterone propionate. Various combinations of these preparations have been used. It is probable that more adequate methods of purifying extracts and further study concerning the chemical nature and synthesis of these and other endocrine preparations will make their use in properly selected cases more successful.

22. Fèvre, M., and Eck, R.: Etude clinique et thérapeutique de l'ectopie testiculaire, *Ann. méd.-chir.* **3**:339, 1938.

23. Thompson, W. O., and Heckel, N. J.: Undescended Testes, *J. A. M. A.* **112**:397 (Feb. 4) 1939.

24. Aberle, S. B. D., and Jenkins, R. H.: Undescended Testes in Man and Rhesus Monkeys, *J. A. M. A.* **103**:314 (Aug. 4) 1934. Cohn, S.: Anterior Pituitary-Like Principle in the Treatment of Maldevelopment of the Testicle, *ibid.* **103**:103 (July 14) 1934. Dorff, G. B.: Maldevelopment and Maldevelopment of the Testes, *Am. J. Dis. Child.* **50**:1429 (Dec.) 1935. Drake, C. B.: Spontaneous Late Descent of the Testis, *J. A. M. A.* **102**:759 (March 10) 1934. McCahey, J. F.: Gonadotropic Hormone Therapy in Cryptorchidism and Disturbances of Spermatogenesis, *Pennsylvania M. J.* **41**:359, 1938. Rea, C. E.: Further Report on Treatment of Undescended Testes by Hormonal Therapy at the University of Minnesota Hospitals: Discussion of Spontaneous Descent of Testis and Evaluation of Endocrine Therapy in Cryptorchidism, *Surgery* **7**:828, 1940. Schapiro, B.: Kann man mit Hypophysenvorderlappen den unterentwickelten männlichen Genitalapparat beim Menschen zum Wachstum anregen? *Deutsche med. Wchnschr.* **56**:1605, 1930. Eisenstaedt, Appel and Fraenkel.^{18c}

It would seem that testes which have failed to descend because of an endocrine imbalance either before birth or in the early years of life might be brought into normal position by adequate physiologic (endocrine) stimulation. The descent of testes which are abnormally located because of anatomic failure and pathologic change will not be affected by endocrinotherapy, and surgical intervention becomes an obvious necessity.

It is possible that the discrepancies in the results of reliable observers are due to: (1) variability in the type, the potency and the dosage of the preparations used; (2) lack of anatomic classification between undescended, maldescended and ectopic testes; (3) lack of selectivity of patients for the type of treatment instituted—that is, physiologic (endocrine) treatment has been given to patients requiring early surgical intervention, and operation has been performed on patients who might have been amenable to physiologic (endocrine) therapy. It is important in deciding the treatment to be used in each case to determine whether various endocrine stigmas, such as infantilism, eunuchoidism or other signs of endocrine abnormality, are present. Patients who appear normal in every respect with the exception of the testes can be considered less suitable for endocrinotherapy. Patients showing signs of underdevelopment due to endocrine insufficiency may show satisfactory progress when adequate doses of the proper preparation or preparations are administered.²⁵

Engle²⁶ stated that in the descent of the testes following endocrinotherapy the subsequent increase in mass and weight are the most important factors. However, he qualified this by stating that the external inguinal ring must be open and the gubernaculum testis must be pulling downward. Browne¹⁷ successfully classified and clarified those abnormal anatomic positions which the testis may assume and also attempted to point out the differentiation between the cases in which the testis will descend spontaneously and the cases in which surgical intervention is inevitable. His classification and observations may be of assistance as a guide to therapy. A more physiologic classification seems to be: (1) undescended testes, those which are found within the normal pathway of descent but for the malposition of which there is no anatomic explanation; (2) maldescended testes, those which are found within the normal course of descent but which are prevented from

25. Moricard, R., and Saulnier, F.: Développement artificiel de l'appareil génital par les esters de testostérone, *Gynécologie* **38**:272, 1939. Oberholtzer, A.: Ormoni testicolari sintetici; loro azione fisiologico ed impiego in terapia, con speciale riguardo alla cura della ipertrofia prostatica, *Arch. ital. di urol.* **15**:181, 1938.

26. Engle, E. T.: Experimentally Induced Descent of the Testis in the Macacus Monkey by Hormones from the Anterior Pituitary and Pregnancy Urine, *Endocrinology* **16**:513, 1932.

entering the scrotum by some abnormality in the pathway, such as adhesions, anatomic abnormalities of the inguinal canal, malattachment of the gubernaculum and herniation; (3) ectopic testes, those which have entered the wrong planes of descent and are off their normal course, in the thigh, the os peroneum or the wall of the abdomen.

Despite the various controversial opinions in the literature on endocrinotherapy, a good deal of evidence has been accumulated to show the value of this type of treatment when properly administered; endocrinotherapy has effect not only on the growth and the development of the testis but on the entire genital apparatus, including the vas deferens, the epididymis and the scrotum.²⁷

Reasons for operation in cases of cryptorchidism are as follows: (1) to introduce the testis into the scrotum (after puberty this is the only location in which the testis will produce both internal and external secretions normal in amount and character); (2) to prevent traumatic derangements of the testis (torsion, direct trauma), which occur much more frequently when the testis is in an abnormal position; (3) to anticipate and prevent malignant tumor of the testis, which occurs much more frequently when the testis is in an abnormal position (although there is still controversy concerning the frequency); (4) to obviate the psychic effects which this abnormality has on the growing boy and the adult man; (5) to serve as a part of the repair of inguinal herniation when present.

In my experience of over ten years on the surgical staffs of several institutions, I have had the opportunity to observe the results of both endocrine and operative treatment in a large number of cases of cryptorchidism.²⁸ It is my observation that neither type of treatment is completely successful in all cases. It is imperative to call attention to the fact that although it is an accomplishment to be able to show a palpable testis in the scrotum, it is equally, if not more, important to have this testis function normally.

An operative procedure which would retain the testis in its normal position (the aim from a surgical point of view) would also be advantageous in those selected cases in which postoperative physiologic (endocrine) therapy is indicated.

A method has been devised which I believe preferable when indicated, whether combined with endocrinotherapy or not. This operative technic is dependent on: (1) the retention of the testis in the scrotum

27. Robson, J. M., and Taylor, H.: Factors Influencing the Functional Development of the Male Gonad, *Proc. Roy. Soc., London*, s.B **113**:251, 1933. Smith, P. E., and Leonard, S. L.: Responses of the Reproductive System of Hypophysectomized and Normal Rats in Injections of Pregnancy-Urine Extracts, *Anat. Rec.* **58**:145, 1934. Engle.²⁶

28. Burdick and Coley.^{2a} Moschcowitz.⁴ Burdick and Coley.¹⁰ Arnheim.²⁰

by the use of a fascial flap reflected from the thigh; (2) the reattachment of a previously malattached gubernaculum; (3) the suturing of the scrotum to the thigh.

OPERATIVE TECHNIC

An inguinal incision is made adequate to expose both the internal ring and the neck of the scrotum (fig. 1 *A*). This must be varied according to the position of the testis.

Division of the fascia of the external oblique muscle down through the external ring is made, care being taken not to enter the hernial sac or injure the testis. The hernial sac is isolated and liberated from the structures of the spermatic cord. The gubernaculum is isolated and left attached, the sac being liberated and cut across near the internal ring and ligated. The distal segment of the sac is incised longitudinally and everted to envelop the cord and the testis and is then closed loosely with a running suture. Liberation of the adhesions between the vessels and the cord, especially of those adhesions about the internal ring, is now carefully carried out. By following the vessels directly upward retroperitoneally with blunt and sharp dissection and by separating all adhesions, the vessels are liberated to allow the use of their greatest length. Although the vas deferens usually has sufficient length, blunt dissection is carried out, retroperitoneally downward and medially, when necessary. After the liberation of the vessels and the vas deferens, their lengths are measured to ascertain the position of the testis in relation to the scrotum.

The scrotal sac is enlarged by manual dilation (a Goodell cervical dilator may be used) to make a bed for the testis, and an incision $1\frac{1}{2}$ inches (3.8 cm.) long is made at its lateral inferior aspect. The gubernaculum testis is then grasped, and the testis is pulled down through the scrotal incision; the distance between the adjacent thigh and the testis is then measured (fig. 1 *B*).

At a site on the adjacent thigh within reach of and close to the scrotal incision an oblique incision $1\frac{1}{2}$ inches (3.8 cm.) long is made from above downward and mesially, and the fascia lata of the thigh is exposed by retracting the lateral margin of this incision.

A fascial flap, 1 inch (2.5 cm.) wide, dependent in length on the distance of the testis from the thigh (anywhere from 1 to 3 inches [2.5 to 7.6 cm.]) is then cut from the lateral aspect of the exposed fascia and reflected medially toward the scrotum. It is important to cut and reflect this flap at such an angle that it points toward the testis in order that the flap will not be twisted at its base. If it is found that a long flap (2 or 3 inches [5 or 7.6 cm.]) will be necessary, $\frac{1}{2}$ inch (1.3 cm.) incisions are made at each end of and at right angles to the incision in the thigh to facilitate exposure of the fascia.

When the fascial flap has been adjusted in length and direction to the position of the testis and the gubernaculum, the posterior lip of the scrotal incision is sutured to the medial lip of the incision in the thigh

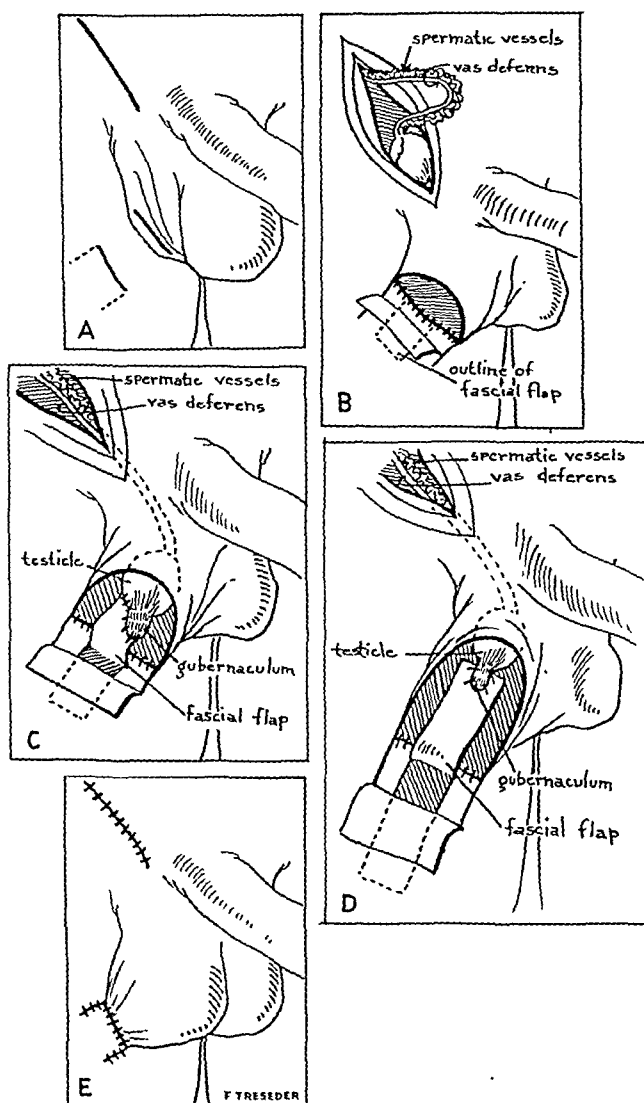


Fig. 1.—First stage of the operative treatment of cryptorchidism. *A*, location of incision; *B*, suture of the scrotum to the medial lip of the incision in the thigh and the outline of the fascial flap; *C*, attachment of the gubernaculum testis and the testicle to the fascial flap; *D*, attachment of the gubernaculum testis to the fascial flap alone; *E*, suture of the scrotum to the lateral lip of the incision in the thigh, thus completing the first stage.

thigh with interrupted sutures, great care being taken to approximate the edges of the skin accurately.

If the testis can be brought down to within $1\frac{1}{2}$ inches (3.8 cm.) of the thigh, the fascial flap is reflected back toward the testis, and

two sutures are placed between the edge of the fascia and the tunica albuginea of the testis. The entire gubernaculum is then placed on the surface of the reflected fascia and attached by two or three carefully placed sutures (fig. 1 C).

If the testis cannot be brought down within $1\frac{1}{2}$ inches (3.8 cm.) of the thigh without undue tension and the intervening distance is $1\frac{1}{2}$ to 3 inches (3.8 to 7.6 cm.) the available gubernaculum alone is placed on the reflected surface of the fascia and sutured to it at whatever points they meet. No sutures are placed between the fascia and the tunica albuginea (fig. 1 D).

The anterior lip of the scrotal incision is now sutured to the lateral lip of the incision in the thigh; and if right angle incisions were necessary, they are closed with interrupted sutures. The scrotum now completely surrounds the anastomosis of the fascia to the gubernaculum and the fascial flap. The wound is dressed with petrolatum gauze (fig. 1 E).

Hernioplasty without transplantation of the cord is now effected by two or three mattress sutures (Ferguson method) to bring the conjoined tendon and the internal oblique muscle of the abdomen to the shelving edge of Poupart's ligament, and the external oblique muscle is closed with a running suture.

The second stage of this procedure is done any time from two to six months later. It consists in incising the skin and the fascial flap through the skin of the thigh leaving the scrotal skin intact and suturing the wounds. Care must be taken to trim and approximate carefully the edges of the scrotal incision.

The advantages of these procedures are as follows: (1) The spermatic cord is kept under constant tension; its length is thus increased, and retraction of the testis is prevented. (2) No foreign material is used for traction, and the fascia used is always available. (3) In cases in which it is not possible to lengthen the cord sufficiently to bring the testis into the thigh, the fascial flap is measured to bridge this gap. In cases of this sort this procedure can be used, even though the original intent was the Keetley-Torek operation. (4) The testis remains in the scrotum, its normal position, and is allowed to develop immediately on completion of the first stage (its sensitivity to temperature changes when out of the scrotum is well known). (5) The second stage is a simple procedure and does not endanger the testis. (6) If endocrinotherapy is indicated, it can be instituted immediately after the first stage, when the testis is in its normal position. (7) If the testis cannot be brought down to within 3 inches (7.6 cm.) of the thigh during the first stage (as it sometimes cannot be in cases of abdominal cryptorchidism), this can be done as a second stage after fixation of the testis to the posterior wall of the inguinal canal as suggested by Cabot.⁶

REPORT OF CASES

CASE 1.—V. C., admitted to the Hospital for Joint Diseases on Sept. 6, 1939, was a well developed white youth, 16 years of age, tall, slender and normal in contour. No endocrine stigmas were noted. Since childhood it had been known that only the left testis was present in the scrotum. The bulge which had been noted in the right inguinal region had grown larger in recent years, and the patient had been advised by the school physician to have his hernia repaired. The patient had no symptoms referable to the abnormal position of the testis. No therapy of any kind had been attempted for this condition.

Physical examination revealed one testis on the left side of the scrotum, about one and a half times the normal size. The scrotum was completely developed on this side. On the right side there was a right indirect inguinal hernia of the congenital type. The scrotal sac on this side was undeveloped and consisted of a slight redundancy of skin into which the hernia protruded. A small mass, the testis, was palpated at the internal ring, apparently having just entered the inguinal canal. It could not be moved further downward by manual effort but was easily reduced into the abdomen with reduction of the hernia. The remainder of the physical and laboratory examinations yielded entirely negative results, with the exception of hypertrophied tonsils.

Operation was performed three days after admission with the patient under general anesthesia. Incision in the right inguinal region revealed a large hernial sac which was easily dissected free of the surrounding tissues after incision of the fascia of the external oblique muscle down through the external inguinal ring.

On opening the hernial sac, the testis (about the size of a small olive) was found lying at the level of the internal ring. The vas deferens and the spermatic vessels, which were closely adherent to the hernial sac, were carefully dissected away, and the sac was divided in its proximal portion and ligated. The adhesions between the spermatic vessel and the vas deferens were separated and divided with blunt and sharp dissection, and both the vessels and the cord were liberated by blunt dissection retroperitoneally along their course. The distal portion of the hernial sac in which the testis lay was opened; the gubernaculum was isolated, and the redundant hernial sac was everted about the cord and the testis with a running suture. By manual dilation the right side of the scrotum was enlarged. It was found that the spermatic vessels and the vas deferens were now long enough to place the testis within the scrotum, although a moderate degree of tension was necessary. The scrotum was then incised, and the testis and the gubernaculum were brought out through the incision. An oblique 2 inch (5 cm.) incision was made in the adjacent thigh, and the fascia lata was exposed. A fascial flap 1 inch (2.5 cm.) wide and $2\frac{1}{2}$ inches (6.3 cm.) long was reflected backward to the gubernaculum.

After the medial lip of the incision in the thigh had been sutured to the posterior lip of the scrotal incision, the gubernaculum was attached to the reflected fascial flap by several interrupted sutures without undue tension. The anterior lip of the scrotal incision was then sutured to the lateral lip of the incision in the thigh with interrupted sutures. The testis was felt in the fundus of the scrotum. The scrotal wound was dressed with petrolatum gauze, and the hernia was repaired by the Ferguson method with three mattress sutures (fig. 2).

After operation, the patient received daily injections for sixteen days of 200 rat units of chorionic gonadotropin. Both wounds healed rapidly. His postoperative course was complicated by a low grade febrile reaction due to tonsillitis; this

began on the twelfth postoperative day. The fever subsided after tonsillectomy. However, this incident and the added operative procedure prolonged his period of hospitalization until November 11.



Fig. 2.—Patient in case 1 after the first stage procedure.



Fig. 3.—Patient in case 1 after the completion of the second stage.

The patient returned to the hospital for a second stage procedure on Feb. 5, 1940. Operation was performed on February 7; it consisted of an incision through the scrotal skin flush with the thigh and an incision of the fascial flap. The wounds in both the thigh and the scrotum were sutured with interrupted sutures. The testis was observed to be approximately twice as large as it was previously and about two thirds the size of a normal testis. It was noted at this procedure that the flap connecting the testis to the thigh had greatly increased in thickness. A section of this tissue showed this increase to be due to hypertrophy of the muscular fibers of the gubernaculum.

Follow-up examination on September 15 revealed the testis to be about four fifths the size of a normal testis (although only two thirds as large as the opposite testicle) and to be freely movable in the scrotal sac (fig. 3).

CASE 2.—J. R., a 17 year old Negro youth, was admitted to the Hospital for Joint Diseases on Sept. 6, 1939, because of bilateral inguinal hernias and the absence of both testes from the scrotal sac. The patient suffered no inconvenience from these abnormalities. Several months prior to admission, he had received a series of injections of an endocrine preparation in an effort to cause descent of his testes, but no change was noted.

Examination revealed a well developed youth of normal size and contour. There were no endocrine stigmas. Both inguinal regions showed herniations of the congenital indirect type. The scrotum was underdeveloped. On the right side the testis was found in the inguinal canal about midway between the internal and the external rings. It could be moved farther downward by manipulation. On the left side the testis was palpated in the inguinal canal just at the internal



Fig. 4.—Patient in case 2 after the first stage procedure on the left side.

ring and could easily be reduced into the abdomen but could not be moved farther downward.

Operation on the left side was performed three days after admission, and a procedure similar to that performed in case 1 was carried out. The testis was observed to be about one half the normal size. The cord was lengthened by dissection. After separation from the hernial sac, the gubernaculum was isolated and found to be fairly large. The testis was brought down through an incision in the scrotum. Both the testis and the gubernaculum were anastomosed to the fascial flap reflected back from the thigh (fig. 4).

After operation there was a moderate amount of infection about the scrotal wound; this was successfully treated with wet dressings. The patient was given thirteen daily injections of 200 rat units each of chorionic gonadotropin and was discharged with wounds completely healed on October 12.

The patient was readmitted for the second stage procedure (already described in the report of case 1) on November 16. A section removed from the fascial flap attached to the gubernaculum showed thickening similar to that previously described. On this admission, it was noted that the testis on the side operated on was now enlarged to about 2.5 cm. in diameter, about two thirds the size of a normal testis, and that it hung freely within the scrotum. Seven injections of



Fig. 5.—Patient in case 2 after the second stage procedure on the left side.



Fig. 6.—Patient in case 2 after bilateral operative procedure; both testes are now in the scrotum.

200 rat units each of chorionic gonadotropin were administered following the second stage. The patient was discharged on November 28 (fig. 5).

The patient's third admission was on Feb. 9, 1940. At this time he was to have the hernia on the right side repaired and the right testis brought down. The left testis was now found to be normal in size and freely movable within the scrotum. The right testis had increased in size within the inguinal canal and had descended almost to the external ring. The operation was performed as previously described. A fascial flap, $1\frac{1}{2}$ inches (3.8 cm.) long, was found sufficient and was anchored both to the testis and to the gubernaculum. The incisions in both the scrotum and the thigh healed rapidly, and the patient was discharged on March 1 after eleven daily injections of 200 rat units each of chorionic gonadotropin. The second stage procedure on the right side was performed on September 21 (fig. 6).

Both testes were observed to be normal in size and free in the scrotum. The patient was discharged on September 24.²⁹

COMMENT

The possibility that abnormalities in the gubernaculum testis or its attachment are an actual or a predisposing cause to abnormal position of the testis has been considered likely by several authorities.²

In both cases reported the gubernaculum was malattached, in that it was densely adherent to the walls of the hernial sac and that the attachment was movable with the reduction of the hernia. Malattachment of the gubernaculum would nullify the effects of the force of the gubernaculum in causing normal descent of the testis. My experience along with that of others in several cases has shown that the further the descent of the testis from the normal position, the greater the persistence, at least in size, of the gubernaculum. In this operative procedure, therefore, the purpose of the attachment of the gubernaculum to the fascial flap is twofold: (1) to assist in retaining the testis in the correct position; (2) to correct the malattachment and give the gubernaculum a new attachment so that the pull is corrected and the force utilized to bring down and maintain the testis in the normal position.

It is of interest to note that from the sections taken from the union of the gubernaculum to the fascial flap in each case during the second

29. Since the completion of this article, the operation described has been performed on 2 patients at the United States Naval Hospital, Brooklyn. One patient was a man 45 years of age. The operation was done concomitantly with herniotomy. At the time of writing it is three months since these procedures were carried out; apparently both were completely successful. The second stage was done seven weeks after the original operations; by that time the testis was free in the lower pole of the scrotum. The second patient was 20 years of age. He had recurrent hernia following an unsuccessful attempt at orchidopexy ten years previously. In this procedure, despite the scarring and adhesions caused by the previous operation, it was possible to bring the testis down to the upper pole of the scrotum from the internal ring and to attach it with a moderate degree of tension to a fascial flap from the thigh. At the time of writing the testis is twice its former size (about one half as large as normal) and the second stage is to be performed in a few weeks.

stage procedure it is evident that the firm adherence of the gubernaculum to the fascia was due to an intermingling between the muscle bundles of the gubernaculum and the fascial fibers (figs. 7 and 8). This is added evidence in the controversy concerning the operative union of these two tissues.³⁰ It was also noted both clinically and microscopically that

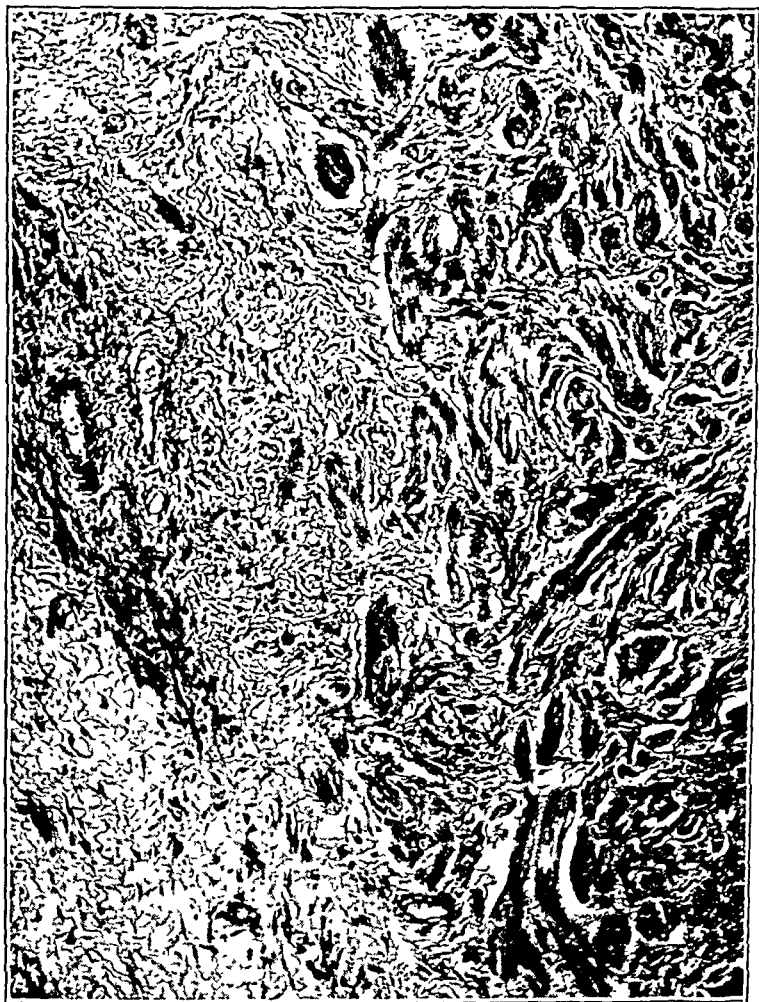


Fig. 7.—Photomicrograph of a section taken through the attachment of the gubernaculum testis to the fascial flap of the patient in case 1.

the muscular fibers of the gubernaculum had increased three or four times their original size. This thickening and increased tension of the gubernaculum followed endocrinotherapy, and it is possible that chorionic gonadotropin exerts an effect on the gubernaculum and indirectly on the

30. Haas, S. L.: The Union of Grafts of Live and of Preserved Fascia with Muscle: A Comparative Study, *Arch. Surg.* **23**:571 (Oct.) 1931.

descent of the testis. In an effort to prove this contention, experimental work with rabbits is now under way, and the result will be published on its completion.

It is worthy of note that both patients were comfortable between the first and second stages of this procedure and were hardly limited in their



Fig. 8.—Photomicrograph of a section taken through the attachment of the gubernaculum testis to the fascial flap of the patient in case 2.

activity. In fact, the patient in case 2 stated that between the first and the second stage on the right side he performed sexual intercourse normally. It is of importance also to report that examination of the semen of this patient after bilateral orchidopexy by the method described showed large numbers of highly mobile spermatozoa.

In the selection of suture material, there is a choice of chromic catgut, silk, linen or cotton. In case 2, silk was used on the right side

and linen on the left. Although clinical observation showed the side with linen to have less tissue reaction and a more mobile flexible scar, a section taken through the area containing the stitches showed that the linen caused a low grade foreign body reaction. In a more recent case, fine cotton proved entirely satisfactory. However, no matter which suture material is chosen, it is my experience that lightness and fineness are of more importance than the type of material used.

A word of warning should also be spoken concerning the use of gonadotropins. Although in competent hands with proper dosage of the correct substance good results may be accomplished in carefully selected cases, the many dangers involved in the use of these powerful agents must be realized. Often useless operative procrastination and permanent endocrine injury may result from lack of knowledge or from careless use of these preparations.³¹

Knowledge of the physiologic and chemical properties of endocrine preparations and their effects on specific tissues is increasing daily. Undoubtedly, when specifically potent and purified products are available and their effects on specific organs are known, the possibilities for intelligent endocrinotherapy will increase.

The surgical procedure which has been presented is suitable for use either with or without adjunctive endocrinotherapy, and I believe that physiologic stimulation should be used only when specifically indicated.

SUMMARY

The possible causes of failure of endocrinotherapy for cryptorchidism have been discussed.

A surgical procedure which can be combined with endocrinotherapy when indicated has been described, and the reports of 2 cases have been given.

The role of the gubernaculum testis in bringing about the descent of the testis, the susceptibility of the gubernaculum to endocrinotherapy and the possible use of this structure in a surgical procedure have been described.

31. Collip, J. B.; Selye, H., and Thomson, D. L.: Histological Changes in the Hypophysis Produced by Chronic Administration of Hypophyseal Extracts, *Proc. Soc. Exper. Biol. & Med.* **31**:682, 1934. Eisenstaedt, Appel and Fraenkel.^{18c}

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BACTERIOSTATIC PROPERTIES OF SULFANILAMIDE AND SOME OF ITS DERIVATIVES

I. SUCCINYLSULFATHIAZOLE, A NEW CHEMOTHERAPEUTIC AGENT LOCALLY ACTIVE IN THE GASTROINTESTINAL TRACT

EDGAR J. POTH, M.D., PH.D.

F. LOUIS KNOTTS, M.D.

JAMES T. LEE, M.D.

AND

FRANK INUI, M.D.

BALTIMORE

A systematic study to find a satisfactory drug to alter the bacterial flora of the intestinal tract was undertaken after it became apparent that sulfanilylguanidine has a limited application in the surgical treatment of diseases of the gastrointestinal tract. Sulfanilylguanidine, according to the original reports of Marshall, Bratton, White and Litchfield¹ and Firor and Jonas,² seemed to offer great possibilities in this field. However, additional experience presented by Firor and Poth³ showed that this drug is not satisfactory because (1) the drug is too readily absorbed from the gastrointestinal tract, giving rise to frequent and occasionally severe reactions, and (2) is ineffectual in the presence of ulcerating lesions of the bowel.

The present investigation was undertaken to find an active drug which is not absorbed from the gastrointestinal tract in sufficient quantities to cause toxic manifestations and which is effective in the presence of ulcerating lesions of the intestinal mucosa. It soon became apparent that to find a drug which is effective in the lumen of the

From the Department of Surgery, Johns Hopkins University School of Medicine.

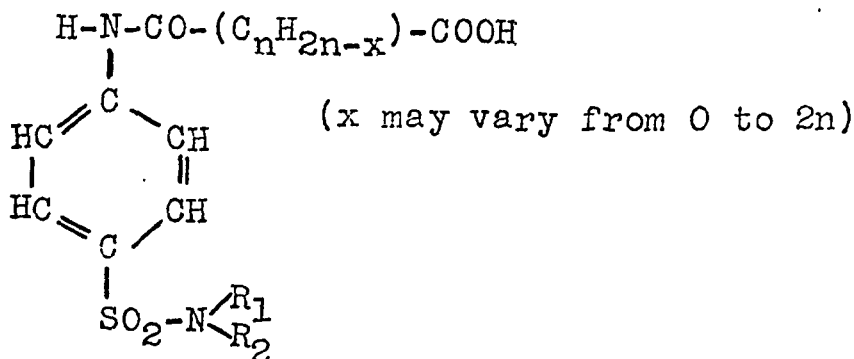
1. Marshall, E. K., Jr.; Bratton, A. C.; White, H. J., and Litchfield, J. T., Jr.: Sulfanilylguanidine: A Chemotherapeutic Agent for Intestinal Infections, *Bull. Johns Hopkins Hosp.* **67**:163, 1940.

2. Firor, W. M., and Jonas, A. F.: The Use of Sulfanilylguanidine in Surgical Patients, *Ann. Surg.* **114**:19, 1941.

3. Firor, W. M., and Poth, E. J.: Intestinal Antisepsis with Special Reference to Sulfanilylguanidine, *Ann. Surg.* **114**:663, 1941.

bowel and is not inhibited by paraaminobenzoic acid ⁴ and like substances, one must discover a compound which is not active through the free amino group of sulfanilamide and its ordinary derivatives or a compound which will attain a high concentration inside the cell of the bacterium, either because of differential absorption or because the concentration of the drug in the medium can be kept at a high level without toxicity to the host. With such a compound it might be possible by mass action to shift the equilibrium away from the paraaminobenzoic acid effect and get activity in the presence of inhibitors. To this end the study of a series of compounds with free carboxyl radicals was undertaken.

A number of substances were found to possess bacteriostatic activity even when the primary amino group on the benzene ring of sulfanilamide or one of its derivatives had been conjugated with dibasic organic acids to form substituted acid amides. The general formula for this series of amic acids can be represented as follows: ⁵



It was observed that the conjugated derivatives were not directly responsible for the local bacteriostatic activity in the gastrointestinal tract. It soon became evident, however, that those compounds which were easily hydrolyzed and consequently resulted in readily absorbed split products gave rise to toxic manifestations, whereas those substances not readily split by mineral acids but requiring sodium hydroxide for saponification were poorly absorbed from the bowel and did not possess toxic properties, although they did have bacteriostatic activity, as was indicated by their effect on the coliform bacteria in the feces. And, what is even more interesting, some of these condensed derivatives were shown to be active in the presence of ulcerations of the mucosa. The presence of the free carboxyl group influences the excretion of compounds of this series by the biliary tract (unpublished data).

In this study the bacteriostatic activity of sulfanilamide and various derivatives and combinations of these compounds (18 drugs in all) was

4. Woods, D. D.: The Relation of Para-Aminobenzoic Acid to the Mechanism of the Action of Sulfanilamide, *Brit. J. Exper. Path.* **21**:74, 1940.

5. Miller, E.; Rock, H. J., and Moore, M. L.: Substituted Sulfanilamides: I. N⁴-Acyl Derivatives, *J. Am. Chem. Soc.* **61**:1198, 1939.

investigated; the results of these experimental studies on dogs are summarized in table 1. From this table it is evident that succinylsulfanilamide and succinylsulfathiazole may be expected to have useful therapeutic applications. The results of these studies on both the experimental animal and on man can best be discussed under three heads: (1) antibacterial activity as shown by the effects on the coliform organism in the stool, (2) absorption and excretion and (3) toxicity.

MATERIALS AND METHODS

Routine Experimental Approach Used in the Study of Each Compound.—Dogs were used exclusively for the feeding experiments. After withholding food for twenty-four hours, a specimen of stool was taken directly from the rectum for a bacterial count. The drug was then given every four hours. The total quantity to be administered in twenty-four hours was weighed and mixed thoroughly with freshly ground meat. This meat was divided into six equal portions and comprised the entire food ration for the animal. Thus the animal received the drug thoroughly mixed with a low residue diet at four hour intervals: 12 m., 4 p. m., 8 p. m., 12 a. m., 4 a. m. and 8 a. m. A stool specimen was taken directly from the rectum daily at 10 a. m. Blood was taken from an ear. Urine was obtained directly by catheterization to avoid contamination with the drug from the highly concentrated feces.

Experience has shown that the first sign of intoxication in the dog is anorexia. If, after the animal has refused to eat, it is forcibly fed, other toxic manifestations may occur, such as vomiting, loss of weight, bloody stools, erythematous rash, conjunctivitis, photophobia, liquefaction of the cornea, irritability, tetany, paralysis and, finally, death. Once an animal had accepted the drugged food, so that refusal because of the taste of the compound or because of the animal's feeding habits was excluded, its failure to eat was considered an early sign of toxicity. The quantity of meat given never exceeded the animals's food requirements.

If the trial daily dosage of 1.0 and 0.5 Gm. per kilogram of body weight in six divided doses gave evidence of good bacteriostatic properties, the efficacy of the drug was further studied with dosages of 0.25, 0.1 and 0.05 Gm. per kilogram per day. In this manner the smallest effective dose was determined and the therapeutic ratio indicated.

Those drugs which gave promise of suitable properties were fed over long periods for studies of chronic toxicity. Finally, extensive gross and microscopic examinations of the tissues were made.

Quantitative Determination of the Drug.—The quantitative estimation of the drug content of the blood, the urine and the stool followed the method of Bratton and Marshall,⁶ which was modified when necessary. Some of the dibasic condensation products are difficult to hydrolyze and frequently require alkaline saponification to free the aromatic amino radical to permit diazotization and subsequent coupling to form the dye for colorimetry. An Evelyn colorimeter was used.

The percentage of drug in the stools is expressed on the basis of the water content of the excreta. A specimen of stool is weighed, dried in a vacuum and

6. Bratton, A. C., and Marshall, E. K., Jr.: A New Coupling Component for Sulfanilamide Determination, *J. Biol. Chem.* **128**:537, 1939.

TABLE 1.—Comparison of the Absorption, Excretion and Toxicity and the Bacteriostatic Activity of Sulfanilamide and a Series of Its Derivatives, as Indicated by the Local Effects on the Coliform Bacteria in the Bowel of the Dog

Compounds	Daily Doses	Concentration of the Drug in the Blood, Mg. per 100 Cc.			Concentration of the Drug in the Urine, Mg. per 100 Cc.			Drug Concentration of the Stool (Gm. Based on Water Content of Feces)	Comparative Action	Toxicity	Comments
		Free	Conjugated	Free	Free	Conjugated	Saturated				
Sulfanilic acid.....	2 2	1.5 1.0	18.0 10.0	22.0 10.0	Saturated	±	±	++	Readily absorbed, giving high blood levels with relatively little effect on coliform organisms in bowel
Sulfanilamide.....	6 6 6	0.25 0.5 1.0	12.0 30.0 50.0	0.55 0.60	++ ++	±	0 0	Some effect on coliform bacteria, but not sufficient even at toxic levels of drug
Sulfadiazine.....	6	1.0	45.0	0.21	++	++	++	Local action insignificant in dosages causing toxic manifestations
Sulfathiazole.....	6	0.25	15.0	...	Crystals	0	+	+	High blood levels of drug without local action
Sulfanilyguanidine....	6 2 5	0.3 1.0 5.0 5.0	5.0 10 to 15 10 to 15 10 to 35	...	Saturated crystals	...	Solid drug	++	++	0	1 Gm. per kilogram per day in six equally divided doses causes moderate drop in coliform organisms in bowel; concentration of drug in blood moderately high; urine saturated; toxic manifestations severe in a large percentage of animals with occurrence of corneal lesions
Maleylsulfanilamide....	6 6 6	0.25 0.5 1.0	2 3 ...	2.0 3.0	500 600	± ++ ++	++ ++ ++	++ ++ ++	Highly toxic, producing anorexia, diarrhea, vomiting, paralysis and death; death may occur after few days; with small doses animals become paralyzed and die weeks after discontinuance of drug
Maleylsulfanilhydrox- imide	2	5.0	++	++	++	Highly toxic, causing vomiting, bloody diarrhea, nephritis and death
Succinylsulfanilamide..	6 6 6 6	0.25 0.5 1.0 2.0 5.0	2.5 2.5 4.0 2.5 2.5	1.6 1.0 1.5 1.5 0.5	210 ...	900 2,100 ...	5.0 5.0 1.0	++ ++ ++ ++ ++	+	0 0 0 ++ ++	Low toxicity; anorexia and vomiting occur with higher dosage levels; causes no deaths; all animals recover immediately after dosage is lowered; high antibacterial activity; animals healthy after 7 weeks' dosage of 1 Gm. per kilogram daily; no tissue lesions occur
Succinylsulfanilamide and sulfanilamide	6 6 6	0.25* 0.25† 0.5*	2.5 2.5	0 0	2.5	...	++	0	Action of succinylsulfanilamide somewhat enhanced by simultaneous administration of sulfanilamide
	6	0.25†	2.5	2.5	5.0	++	++	0	

Succinylsulfanilamide and sulfadiazine	6	0.5	45	...	4.0	8.0	+++	0	Simultaneous administration of sulfadiazine with succinylsulfanilamide enhances activity of latter; blood concentration becomes rather elevated
Succinylsulfanilhydrox- amide	2	0.5	+++	+++	Extremely toxic, causing bloody diarrhea and extensive gastroenteritis
Succinylsulfathiazole	6	0.5	0	0	Low toxicity; only toxic manifestation observed was anorexia after high dosages; for 5 weeks showed no evidence of toxicity; during this entire period coliform bacteria were at extremely low levels; extensive tissue studies revealed no abnormalities
Sulfathiazole and succinylsulfathiazole	6	0.25†	11.4	+++	+	Simultaneous administration of sulfathiazole with succinylsulfathiazole augments effect on coliform organisms in bowel (chart 5); some of sulfathiazole in blood
Succinylsulfanilamido- ethylthiazolidone	6	0.10§	++	+	
Succinylsulfapyridine	6	0.25†	13.2	1.83	6.5	+++	+	
Succinylsulfadiazine	6	0.50§	12.0	1.4	+++	+	
Succinylsulfanilyguanidine	6	0.5	...	6	+++	+	Moderately toxic; anorexia develops by third day; compound has fair degree of antibac- terial activity
	6	1.0	...	10	+++	+	While this drug has moderate antibacterial activity, it is too toxic for large doses
	6	2.0	...	4	+++	+	Too toxic at doses having antibacterial activity
	6	0.5	...	23	+++	+	
	6	1.0	+++	+	
	6	0.05	0	0	While this drug has exhibited no toxicity under the conditions studied, it does not appear to be a satisfactory compound, because even though it promptly reduces the coliform count, it fails to keep the count down; after a week the effect completely disappears
	6	0.10	0	0	Low toxicity; antibacterial activity not pro- nounced
	6	0.25	0	0	
	6	0.50	0	0	
	6	1.0	0	0	
Succinylsulfamethyldiazine	6	0.5	0	0	
	6	1.0	0	0	

* Succinylsulfanilamide.
† Sulfanilamide.
‡ Sulfathiazole.
§ Succinylsulfathiazole.

reweighed. The difference in weight gives the quantity of water. The dried stool is suspended in water, and the drug content of an aliquot part is determined.

$$\frac{\text{Weight of the drug in the stool}}{\text{Weight of the water in the stool}} \times 100 = \frac{\text{Percentage of the drug based on}}{\text{the water content of the stool}}$$

This notation is used because the quantity of the drug compared with the water content of the stool determines the degree of saturation. There is a wide variation in the water content because an effective drug of this series modifies the stool considerably.

Bacteriologic Studies.—Stool specimens were taken at frequent intervals directly from the rectum of the experimental animal and from the freshly expelled feces of the patient. It is important that the stool specimens be chilled immediately and kept cold, because once the feces are expelled, the bacteria might multiply rapidly at room temperature. A quantity of feces which, depending on its consistency, would give approximately 1 cc. of sediment was emulsified and suspended in 10 cc. of sterile physiologic solution of sodium chloride and then centrifuged for fifteen minutes at a speed of 1,700 revolutions per minute. The amount of sediment was read, and dilutions were made based on this value. One cubic centimeter of sediment was considered equivalent to 1 Gm. of wet stool. All counts were made on pour plates. Desoxycholate agar was used for differentiating *Bacillus coli*, and plain infusion broth agar plates were employed for making total aerobic bacterial counts.

B. coli, *Bacillus proteus*, *Bacillus pyocyaneus*, *Aerobacter aerogenes* and *Streptococcus faecalis* can be identified in the desoxycholate agar medium. No further identification was practical. The drugs which possess the greater bacteriostatic activity frequently caused the total number of aerobic bacteria to decrease by more than the mere drop due to the fall in the number of coliform organisms. Ordinarily the number of aerobic bacteria would be one thousand to ten thousand times that of *B. coli*.

It is interesting to note that as the *B. coli* flora decreased to low numbers, *B. proteus* frequently began to grow out, increasing at times to 1,000 to 10,000 colonies per gram of wet stool. *A. aerogenes* would occasionally grow out as *B. coli* disappeared. This phenomenon causes considerable confusion because the appearance of the deep colonies of these two strains of organisms in the desoxycholate medium is identical. An attempt was made to count these bacteria differentially by the ratio of the surface colonies, which are distinguishable by their characteristic growth.

OBSERVATIONS ON SUCCINYLSULFANILAMIDE ⁵

Table 1 shows succinylsulfanilamide to have excellent bacteriostatic activity and low toxicity. This compound has a solubility of 3.5 Gm. per hundred cubic centimeters of water at 20 C. Dogs receiving this drug in sufficient amount to cause excellent lowering of the coliform organisms show average blood levels of 2.5 mg. per hundred cubic centimeters for sulfanilamide and 1.5 mg. per hundred cubic centimeters for succinylsulfanilamide. The concentrations in the urine, however, reach 350 and 2,400 mg. per hundred cubic centimeters, respectively. Since these concentrations are less than the solubilities of these compounds in the urine, no crystals are present. Animals receiving 2 to 5

Gm. per kilogram daily at four hour intervals show mild toxic symptoms of anorexia and vomiting. Two animals were fed 1 Gm. per kilogram daily in six divided doses for ninety-five days. The stools of these animals were practically free of coliform organisms for this period, and toxic manifestations did not develop. Extensive examination of the tissues, both gross and microscopic, revealed no abnormalities.

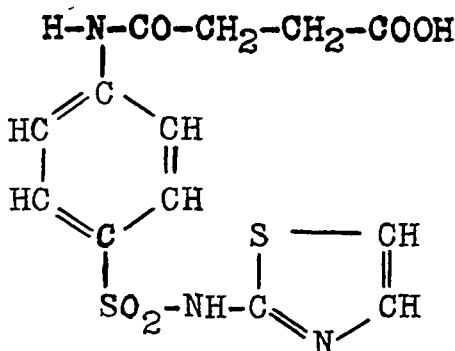
The effect of the simultaneous administration of sulfanilamide and succinylsulfanilamide was studied. The conclusion was that the addition of sulfanilamide did not appreciably enhance the local action of the succinyl derivative.

Succinylsulfanilamide was administered to 3 patients in a dosage of 0.15 Gm. per kilogram daily in six divided doses. The blood levels averaged 2.0 mg. of succinylsulfanilamide per hundred cubic centimeters, and a maximum of 15.0 per cent of the ingested drug was excreted in the urine by 1 patient. With this dosage there was no appreciable effect on the coliform bacteria in the stools. Because of the relatively high absorption of the drug, its use was abandoned, although no toxic symptoms had developed.

OBSERVATIONS ON SUCCINYLSULFATHIAZOLE

Preliminary experimental studies showed succinylsulfathiazole to be most promising. It has strong antibacterial action, is poorly absorbed from the gastrointestinal tract and has not produced toxic manifestations when given in therapeutic doses.

N⁴-succinylsulfathiazole ⁷ may be represented as follows:



It has a solubility of 70 mg. in 100 cc. of water at 37 C. The solubility in urine obviously varies considerably with the p_H and the buffer capacity of an individual specimen because of the readiness with which the free carboxyl group enters into salt formation. The compound is a relatively strong acid, decomposing sodium bicarbonate in aqueous solution. The

7. N⁴-succinylsulfathiazole is registered under the proprietary name of sulfa-suxidine by Sharp & Dohme, Philadelphia.

sodium salt is highly soluble. A syrupy 50 per cent aqueous solution of the sodium salt will crystallize after standing for seven to ten days at 0 C. The succinic acid radical is split off with difficulty, requiring two hours' digestion on a water bath in half-molar sodium hydroxide to effect quantitative saponification and liberation of the primary amino group. A 25 per cent aqueous solution of the sodium salt is stable; it showed no appreciable hydrolysis after six weeks at 37 C.

Activity in Vitro.—Dr. W. Barry Wood compared this compound with sulfanilamide and some of its derivatives as regards their bacteriostatic activity in vitro against a standard strain of *B. coli* in a synthetic medium and found the following approximate relations:

Sulfanilamide	1 (unit)
Sulfanilylguanidine	2
Succinylsulfathiazole	0.1
Sulfapyridine	20
Sulfadiazine	20
Sulfathiazole	50

Furthermore, paraaminobenzoic acid completely inhibits the bacteriostatic activity of succinylsulfathiazole. The activity in vitro shown might have been due to the presence of a small amount of free sulfathiazole in the sample studied. Theoretically, unaltered succinylsulfathiazole should have no activity in vitro.

Antibacterial Activity in the Gastrointestinal Tract.—The bacteriostatic activity of succinylsulfathiazole as measured by its effect on the coliform organisms of the bowel has been studied with varying dosages (table 1) in 35 dogs. When given in adequate amounts, succinylsulfathiazole has not failed to lower the coliform count significantly. The character of the stools changes greatly. They become soft, contain undigested food, have a gelatinous appearance and are practically odorless. Diarrhea is not present. Chart 1 shows the characteristic effects with various dosages.

To study the effect of the presence of ulcerating lesions in the bowel on the bacteriostatic properties of the drug, sloughing lesions were produced in the colon through the destruction of large areas of mucous membrane with liquid phenol by proctoscopy. The drug was equally effective in the presence of these lesions (chart 2).

The simultaneous oral administration of sulfathiazole, which is readily absorbed, and succinylsulfathiazole, which is sparingly absorbed, produces an effect which appears to be a synergistic action of the two drugs (table 1 and chart 3).

Absorption and Excretion.—Since the toxic manifestations of any particular compound must be due not merely to the concentration attained

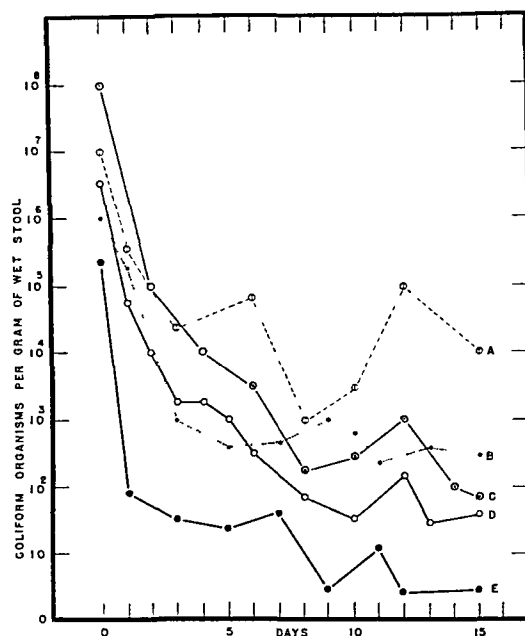


Chart 1.—The effect of various dosages of succinylsulfathiazole on the coliform bacteria in the gastrointestinal tract of the dog. Each curve is based on the average effects observed in from three to five experiments. *A* represents the results after the oral administration of 0.05 Gm. per kilogram daily, given in six equal doses at four hour intervals; *B*, 0.1 Gm. per kilogram; *C*, 0.25 Gm. per kilogram; *D*, 0.5 Gm. per kilogram; *E*, 1.0 Gm. per kilogram.

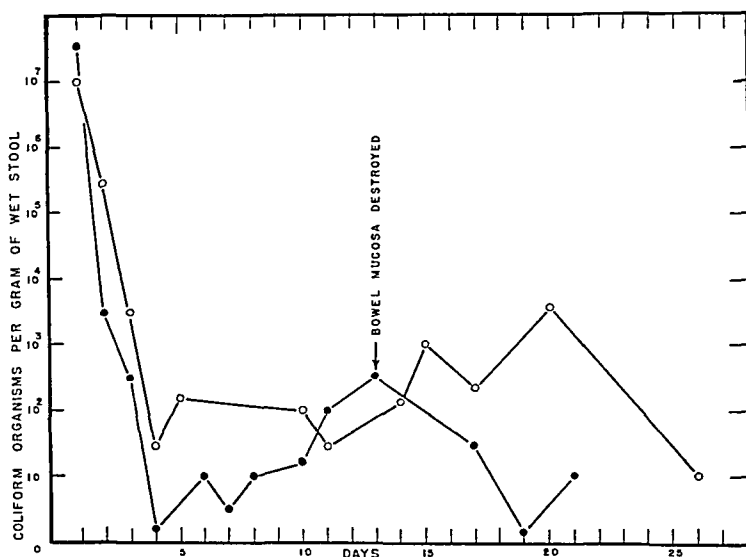


Chart 2.—To demonstrate the effect of lesions of the mucous membrane on the antibacterial activity of succinylsulfathiazole, the number of coliform organisms was reduced by the administration of the drug. Then the mucosa of a large area of the descending colon of the dog was destroyed by cauterization.

in the blood and tissues but also to the absolute quantity absorbed from the gastrointestinal tract and excreted by the kidneys after oral administration, the concentration and the amount of the drug excreted in the urine must be observed (charts 4 and 5). The concentration of the drug in the urine can be determined from specimens obtained directly from the bladder by catheterization, but the total urinary output of the drug over a period cannot be estimated readily because of inability to collect the urine without contamination by feces containing relatively much larger quantities of drug (table 1). One must therefore be content with the determination of the urinary concentration as a guide in the

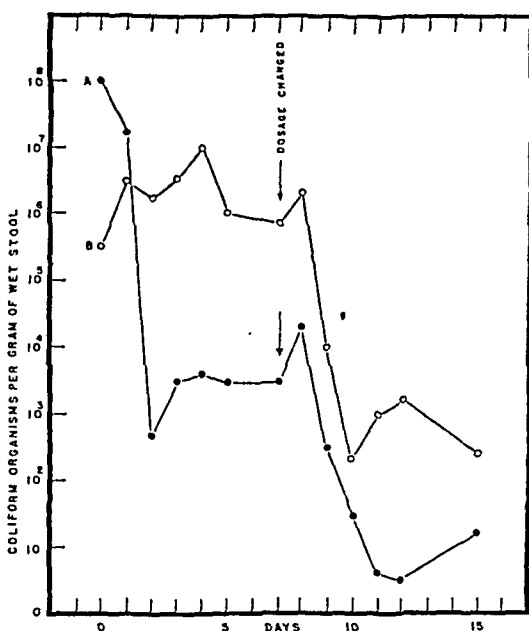


Chart 3.—A demonstration of the apparently synergistic action of sulfathiazole and succinylsulfathiazole when simultaneously administered to the dog. *A* received daily 0.25 Gm. of succinylsulfathiazole per kilogram in six doses for seven days. At this time a daily dose of 0.25 Gm. of sulfathiazole per kilogram was added. *B* received 0.25 Gm. of sulfathiazole per kilogram daily for seven days; then succinylsulfathiazole was added so that the animal thereafter took 0.25 Gm. per kilogram of each drug daily.

experimental animal and must reserve the quantitative output of the drug to be determined on patients receiving the compound after it has been proved otherwise suitable for human use. On an average, a dog receiving 1 Gm. per kilogram daily in six divided doses will have a concentration of 3.5 mg. per hundred cubic centimeters for sulfathiazole and 5.0 mg. per hundred cubic centimeters for the conjugated compound in the blood, while the respective concentrations in the urine are 360

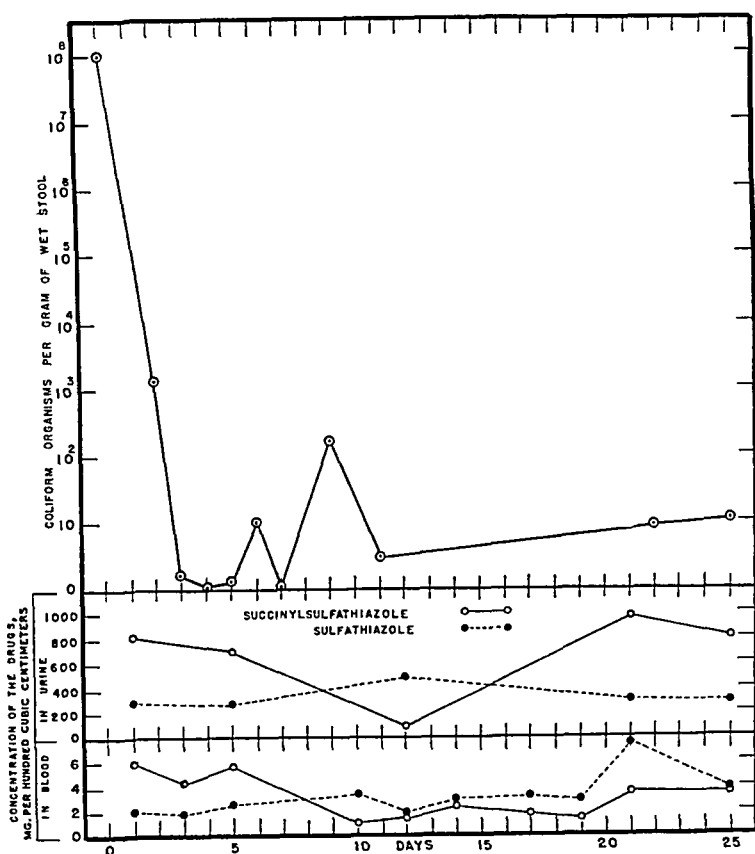


Chart 4.—The significant lowering of the number of coliform bacteria in the bowel of the dog after the daily oral administration of 1 Gm. per kilogram of succinylsulfathiazole divided into six equal doses. The concentrations of the drug in the blood and the urine are given. The degree to which hydrolysis of succinylsulfathiazole is effected to yield sulfathiazole is indicated by the concentration of the latter in the blood and the urine.

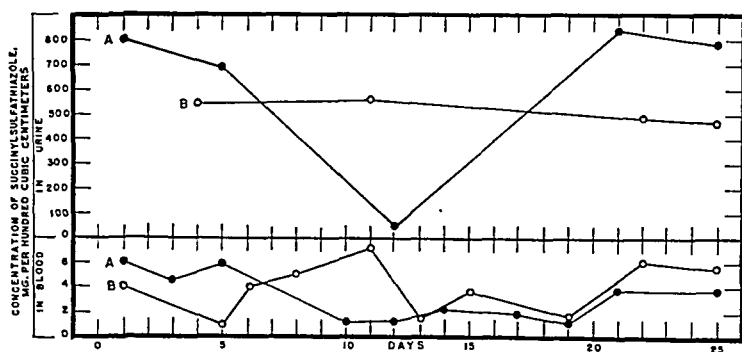


Chart 5.—Illustration of the fact that an animal (A) receiving daily 1 Gm. of succinylsulfathiazole per kilogram divided into six equal oral doses has essentially the same concentration of the drug in its blood and urine as another animal (B) similarly receiving a dosage of 0.25 Gm. per kilogram.

and 600 mg. per hundred cubic centimeters. With this dose the concentration in the stools will average 5 per cent (table 1).

Toxicity in the Dog.—This drug and its sodium salt are so poorly absorbed that, regardless of the dose, no acute toxicity can be demonstrated after oral administration. The acid is rapidly absorbed from the peritoneal cavity, and after intramuscular administration, although the concentration of the drug in the blood is considerable, no toxic manifestations occur (charts 7 and 8). There is some local tenderness after intraperitoneal and intramuscular injection of a water suspension of the solid drug. Laparotomy done a few days after intraperitoneal

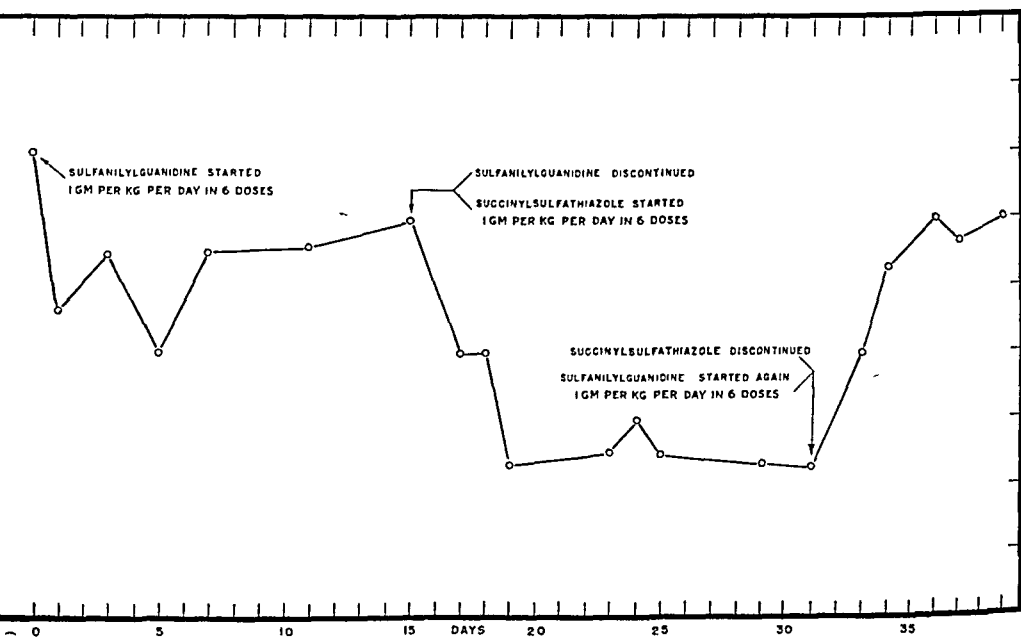


Chart 6.—The relative antibacterial activity of sulfanilylguanidine and succinylsulfathiazole as demonstrated by the effects of these drugs on the coliform organisms in the bowel of the dog.

administration shows the peritoneal cavity to be normal and free of adhesions.

The monosodium salt of succinylsulfathiazole in solution suitable for intravenous administration is readily prepared by the addition of the stoichiometric quantity of sodium bicarbonate to the free acid, succinylsulfathiazole.

Five grams per kilogram of succinylsulfathiazole converted to the sodium salt and given intravenously as a 40 per cent solution causes vomiting in about three to five minutes followed by defecation and collapse. Tetanic seizures accompanied by deep cyanosis develop shortly. This dose is fatal in two hours. At necropsy the concentration

of the free drug in the blood is 30 mg. per hundred cubic centimeters, and the conjugated compound is present in a concentration of 600 mg. per hundred cubic centimeters.

The intravenous administration to 5 dogs of 1 Gm. per kilogram of the sodium salt in a 15 per cent solution caused nausea, and the animals vomited once after ten to fifteen minutes. No further toxic

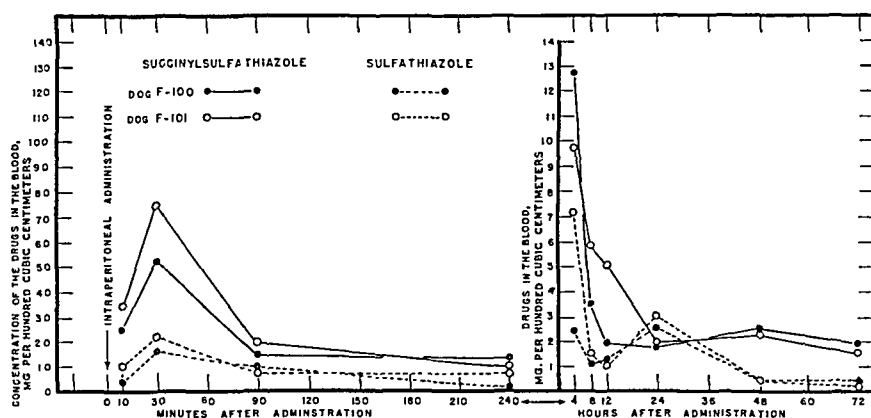


Chart 7.—Illustration of the rapid rate of absorption after the intraperitoneal injection of an aqueous suspension of 1 Gm. per kilogram of succinylsulfathiazole and the rate of its disappearance from the blood.

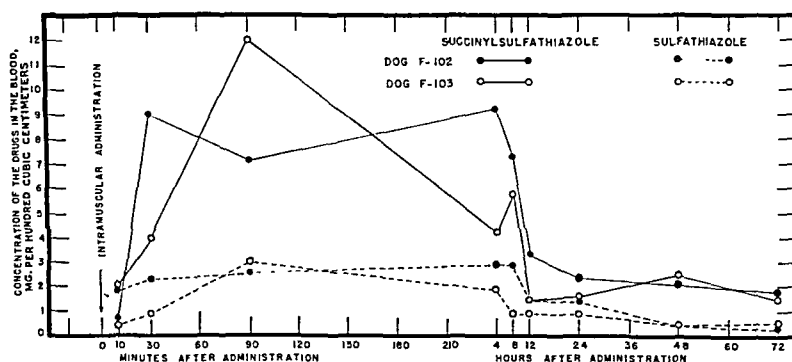


Chart 8.—The concentration of sulfathiazole and succinylsulfathiazole in the blood after the intramuscular administration of an aqueous suspension of 1 Gm. per kilogram of succinylsulfathiazole.

symptoms occurred. The concentration of the drug in the blood and the rate of urinary excretion are presented graphically in chart 9. Complete gross and microscopic examination of the tissues showed no anatomic abnormalities. The intravenous administration of 1 Gm. per kilogram daily for ten days caused the usual vomiting immediately after administration of each dose. Anorexia and increased salivation

sometimes occurred after the second or third dose. The concentration of the drug in the saliva was low, 0.6 mg. per hundred cubic centimeters. These animals showed no additional toxic manifestations. Comparison of specimens of the liver taken before treatment and at necropsy after ten days of repeated daily intravenous injections of 1 Gm. per kilogram of the sodium salt of succinylsulfathiazole showed no histologic changes in the liver cells. The urine sometimes contained as much as 11,000 mg. per hundred cubic centimeters of the drug after intravenous, intraperitoneal and subcutaneous administration of 2 Gm. per kilogram daily of the sodium salt of succinylsulfathiazole for several days. At this high concentration the urine in some cases was clear and had a p_H of

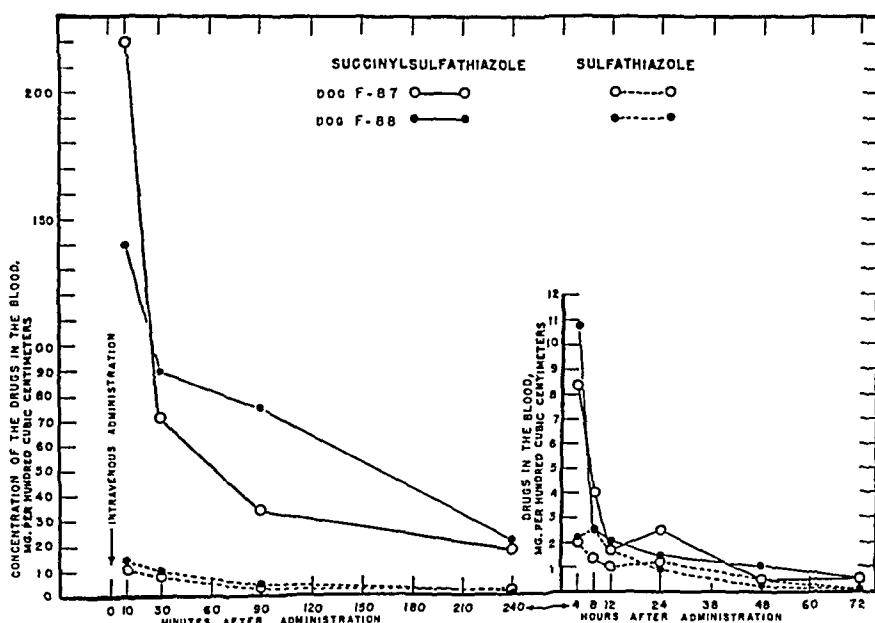


Chart 9.—The rapidity with which the drug disappears from the blood after the intravenous injection of 1 Gm. per kilogram of the sodium salt of succinylsulfathiazole.

6.8. The addition of mineral acid, however, caused the urine to solidify by the precipitation of the relatively insoluble acid form of succinylsulfathiazole.

Dogs receiving 1 Gm. per kilogram daily of succinylsulfathiazole in six divided doses for as long as thirty-five days ate regularly, gained weight and showed no tissue changes on gross and microscopic examination. Concretions of the drug in the kidneys and bladder did not occur. Thirty dogs received the drug in doses as high as 2 Gm. per kilogram daily over a period of several weeks.

Administration to Man.—After obtaining evidence from the laboratory animal indicating the low toxicity and the possible therapeutic

value of succinylsulfathiazole, trial administration of the drug to human beings was undertaken. Normal persons with intact mucous membranes of the gastrointestinal tract were given single doses and then doses of varying amounts at four hour intervals. These persons were kept under close observation, and daily studies of the blood, the urine and the stool were made.

The results of these studies are summarized in table 2. This tabulation shows that the drug is poorly absorbed by man. The quantity of drug excreted in the urine over a period of days varies from 3 to

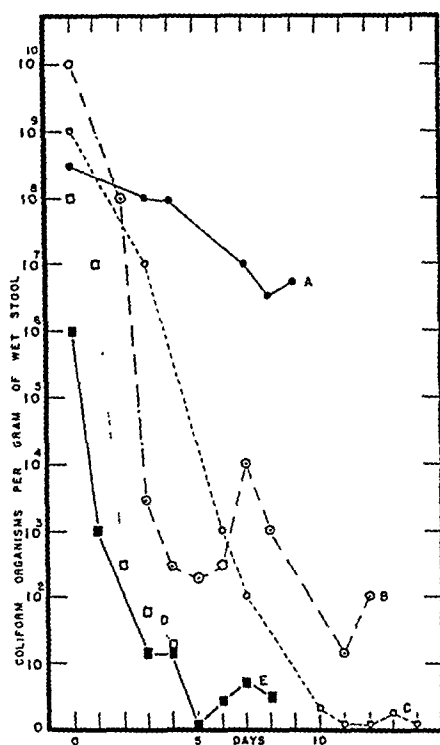


Chart 10.—The effect of varying dosages of succinylsulfathiazole on the coliform bacteria in the gastrointestinal tract of man: *A* diagrams the results of the oral administration of 0.1 Gm. per kilogram divided into six equal doses. *B* represents the effect of the similar administration of 0.2 Gm. per kilogram; *C*, the effect of 0.25 Gm. per kilogram; *D*, the effect of an initial dose of 0.25 Gm. per kilogram followed after four hours by 0.25 Gm. per kilogram per day in six equally divided doses (this patient had large ulcerating carcinoma of the rectum); *E* represents the course after the oral administration of three massive doses of 0.25 Gm. per kilogram at four hour intervals followed by 0.25 Gm. per kilogram per day divided into six equal quantities.

9 per cent of that ingested. On an average 5 per cent of the ingested drug is recovered in the urine.

Examination of chart 10 shows the average therapeutic dose required to alter the bacterial flora of the bowel significantly to be 0.25 Gm. per

TABLE 2.—*Effects of the Oral Administration of Succinylsulfathiazole on Human Beings with Normal Intact Mucous Membranes of the Gastrointestinal Tract*

Patient and Weight, Kg.	Day and Time	Daily Dose Given in Six Equal Fractions, Gm.	Concentration of Drug in Blood		Daily Urinary Output, Gm.		Concentration of Drug in Stools, Gm. per 100 Cc.	Comment
			Free	Conjugated	Free	Conjugated		
N. K. 70	1	35.00	Patient had a normal gastrointestinal tract; he was given a single dose of succinylsulfathiazole equivalent to 0.5 Gm. per Kg.; coliform count dropped from 10^6 to 10^4 ; 4.8% of ingested drug was excreted in urine; no evidence of toxicity
	8:00	(in one						
	12:00	single	1.50	0.90				
	4:00	dose at	1.30	1.60				
	8:00	8 a.m.)	0.96	1.90	1.30	
	2	0.30	1.50	0.47	0.43		
	3	0.40	1.00	0.09	0.46	2.00	
K. A. 61	4	0.00	0.00	0.00	0.00		Normal bowel; received 0.1 Gm. per Kg. daily in six divided doses; coliform organisms dropped from 10^8 to 10^6 ; drop not considered significant; dosage insufficient; 6% of ingested drug excreted in urine; no toxic manifestations
	1	6.00	0.03	0.02	
	2	6.00	0.10	0.05		
	3	6.00	0.80	1.70	0.14	0.22		
	4	6.00	0.50	2.60	0.23	0.10	0.26	
	5	6.00	0.40	1.70	0.12	0.34		
	6	6.00	0.40	2.60	0.03	0.04	0.88	
	7	6.00	0.20	0.26	1.90	
	8	6.00	0.90	1.90	0.14	0.10		
	9	6.00	0.14	0.18	1.04	
	10	6.00	0.50	0.80	0.14	0.25	0.60	
H. L. 50	11	0.30	0.40	0.80	Patient convalescing; normal bowel; received equivalent of 0.18 Gm. per Kg. of succinylsulfathiazole daily; coliform count in stools dropped from 10^7 to 16 colonies per Gm. of wet stool and was maintained at a low level for six days; no toxic manifestations; 9.05% of ingested drug was excreted in urine
	1	9.00	0.48	0.60	
	2	9.00	0.80	8.00	0.30	1.70	0.60	
	3	9.00	0.84	6.50	0.14	0.13	0.56	
	4	9.00	1.30	4.50	0.16	0.16	0.60	
	5	9.00	1.30	5.00	0.35	0.40	2.70	
	6	9.00	1.30	3.60	0.19	0.16	3.30	
	7	9.00	0.80	7.40	0.23	0.14		
	8	0.00	0.80	1.70	0.11	0.09	0.36	
	9	0.00	0.80	1.80	0.12	0.00	0.43	
	10	9.00	2.40	7.30	0.44	0.19	0.57	
	11	9.00	0.22	0.22	0.84	
	12	9.00	1.00	2.30	0.23	0.07	3.88	
G. B. 83	13	9.00	0.80	1.40	0.27	0.56	1.49	Postoperative hernia; normal gastrointestinal tract; received equivalent of 0.2 Gm. per Kg. succinylsulfathiazole daily; stool count for coliform bacteria dropped from 10^9 to 0 and remained below 10^1 for last 6 days that patient was under observation; 5.33% of ingested drug excreted in urine; no toxic manifestations
	1	16.50	2.90	2.00	0.23	0.28	
	2	16.50	2.00	2.60	0.25	0.40		
	3	16.50	2.20	0.50	0.19	0.38	1.10	
	4	16.50	0.80	7.30	0.16	0.33		
	5	16.50	0.80	1.20	0.37	0.91		
	6	16.50	0.16	0.23		
	7	16.50	0.80	1.20	0.26	0.43	2.80	
	8	16.50	0.80	1.20	0.18	0.39	5.06	
	9	16.50	0.50	2.30	0.22	0.57		
	10	16.50	0.80	1.70	0.73	0.73	6.51	
	11	16.50	1.30	4.30	0.38	0.78	3.05	
	12	1.20	1.40	3.00	
R. E. 60	13	6.50	Normal gastrointestinal tract; given initial dose of 0.5 Gm. per Kg. followed by maintenance dosage of 0.2 Gm. per Kg. daily; coliform bacteria count dropped to 50 organisms per Gm. of wet stool; 3.5% of ingested drug was excreted in urine; no toxic manifestations
	1	36.00	
	(at 8 a.m.)							
	12:00	1.30	2.10				
	4:00	0.80	1.40				
	8:00	1.00	3.90	0.20	0.33	3.00	
	2	12.00	0.80	3.50	0.16	0.39	9.20	
	3	12.00	0.50	3.30	0.57	0.16	2.90	
	4	12.00	1.10	2.10	0.41	0.26	1.00	
	5	12.00	1.30	1.90	1.90	
L. Y. 75	6	12.00						Normal bowel; initial dose of 32 Gm., then maintenance dosage of 0.25 Gm. per Kg. per day; B. coll count dropped to 20 organisms per Gm. of wet stool; 4.41% of ingested drug excreted in urine; no toxic manifestations
	1	44.00	0.35	0.12	
	2	18.00	1.00	1.20	0.46	0.50		
	3	18.00	1.00	1.20	0.38	0.37	0.00	
	4	18.00	0.84	0.87	0.53	0.63	1.20	
	5	18.00	0.42	1.00	0.41	0.39	9.10	
	6	18.00	0.42	2.80	0.53	0.43	6.30	

TABLE 2.—*Effects of the Oral Administration of Succinylsulfathiazole on Human Beings with Normal Intact Mucous Membranes of the Gastrointestinal Tract—Continued*

Patient and Weight, Kg.	Day and Time	Daily Dose Given in Six Equal Fractions, Gm.	Concentration of Drug in Blood		Daily Urinary Output, Gm.		Concentration of Drug in Stools, Gm. per 100 Cc.	Comment
			Free	Conjugated	Free	Conjugated		
T. Y. 70	1	9.00	Normal bowel; given 0.25 Gm. per Kg. daily; the B. coli count dropped from 10 ⁹ to 100 per Gm. of wet stool; 5.2% of ingested drug excreted in urine; no toxic manifestations
	2	18.00	0.99	0.51	0.22	0.25	
	3	18.00	0.80	1.40	0.68	0.80	4.40	
	4	18.00	0.60	1.70	0.40	0.52	2.90	
	5	18.00	0.67	1.06	6.80	
	6	18.00	1.08	0.80	0.30	0.43	1.60	
	7	18.00	1.00	4.00	0.32	0.33	1.70	
	8	18.00	0.50	2.40	0.30	0.36	
	9	18.00	1.20	1.05	0.37	0.34	
	10	18.00	0.80	1.20	0.30	0.40	
	11	18.00	0.80	1.20	0.20	0.20	3.60	
	12	18.00	0.40	1.70	
M. R. 75	1	69.00	0.46	1.07	Normal bowel; received 0.75 Gm. per Kg. during first eight hours of administration of drug; there was no marked elevation of blood level of drug; B. coli count dropped from 10 ⁸ to 115 per Gm. of wet stool; there were no toxic manifestations; 4.5% excreted in urine
	2	18.00	1.30	1.80	0.23	0.44	8.83	
	3	18.00	1.40	0.50	0.46	1.58	13.90	
	4	18.00	1.00	1.40	12.20	
	5	18.00	0.12	2.70	5.70	
T. N. 64	1	23.50	0.25	0.26	0.20	Normal bowel; received an initial dose of 0.25 Gm. per Kg. followed by 0.25 Gm. per Kg. per day in six divided doses; coliform organisms dropped from 10 ⁹ to as low as 300 per Gm. of wet stool; 5.5% of ingested drug was excreted in urine
	2	15.00	2.60	3.10	0.94	0.88	
	3	15.00	1.50	1.80	0.22	0.25	0.72	
	4	15.00	1.50	3.20	1.84	0.27	3.00	
	5	15.00	0.90	2.20	0.13	0.22	
	6	15.00	0.90	2.20	0.20	0.30	
	7	15.00	0.30	0.42	8.40	
	8	15.00	0.40	1.40	0.17	0.35	5.10	
	9	15.00	0.15	0.35	
	10	15.00	0.60	1.50	0.34	0.61	
	11	15.00	1.00	1.60	0.39	0.29	4.30	
	12	15.00	0.15	0.20	
	13	15.00	0.60	1.40	0.96	0.80	6.60	
	14	15.00	
C. M. 42	1	9.25	0.14	0.04	0.00	Normal bowel; received 0.25 Gm. per Kg. and an initial dose followed by a maintenance dose of 0.25 Gm. per Kg. daily in six doses; the coliform organisms dropped from 10 ⁹ to 10 ³ ; although this is a 10,000 fold drop, it is not a satisfactory result; an explanation for this failure is not apparent; 6.4% of ingested drug was excreted in urine; no toxic manifestations
	2	10.50	0.40	0.13	
	3	10.50	0.10	1.70	0.09	0.13	5.50	
	4	10.50	0.04	0.04	
	5	10.50	0.20	0.69	0.11	0.16	
	6	10.50	0.40	1.50	0.35	0.31	1.67	
	7	10.50	0.43	0.46	
	8	10.50	0.60	0.60	0.56	0.58	
	9	10.50	0.03	0.04	
	10	10.50	3.60	0.87	0.72	0.59	
	11	10.50	0.26	0.21	
	12	10.50	0.40	1.60	0.82	0.65	
	13	10.50	0.27	0.55	
	14	10.50	1.30	0.00	1.10	0.07	

kilogram per day, administered orally in six equal quantities at four hour intervals. Experience has shown this to be the minimum dose which can be expected to give significant lowering of the coliform bacteria. The routine procedure adopted consists of administering 0.25 Gm. per kilogram in a single initial dose followed by 0.25 Gm. per kilogram daily as stated before. This amount will cause significant lowering of the coliform count of the stools in one to seven days.

Obviously, the effective dose will vary with the condition of the bowel, and it is frequently advantageous to administer 0.5 Gm. per kilogram daily. As much as 1 Gm. per kilogram daily has been given to patients with severe dysentery without ill effects. The administration of 0.25 Gm. per kilogram daily, but given at one hour intervals, did not accelerate the rate of lowering of the coliform bacteria in the stools. However, this frequency of administration did increase the quantity of the drug absorbed and excreted to about twice the amount observed when the same total amount of drug was given at four hour intervals.

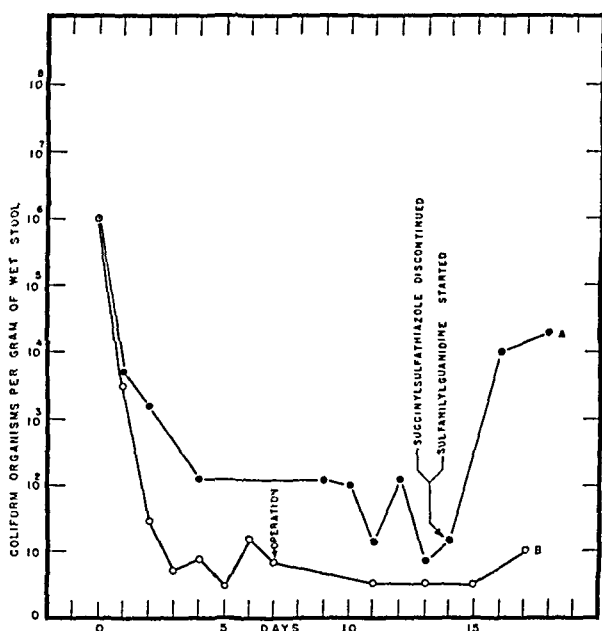


Chart 11.—The relative antibacterial activity of succinylsulfathiazole and sulfanilylguanidine as demonstrated by the effects of these drugs on the coliform organisms in the bowel of man after oral administration. *A* received 0.25 Gm. of succinylsulfathiazole per kilogram daily in three equal doses for fourteen days. This dosage was discontinued, and the maximum recommended dosage of sulfanilylguanidine, 2 Gm. every four hours, was started immediately. *B*, after receiving 10.5 Gm. of sulfanilylguanidine daily for fourteen days had 1,000,000 *B. coli* per gram of wet stool as indicated on day 0 of the chart. The curve indicates the course after the daily oral administration of 0.33 Gm. per kilogram of succinylsulfathiazole. *A* had an intact normal gastrointestinal tract; *B* was suffering from chronic ulcerative colitis.

As the bacterial flora is altered by the action of the drug, the character of the feces changes. The stools become semifluid. Ordinarily, diarrhea does not occur. The feces become relatively odorless and contain more than the normal quantity of mucus. The bulk of fecal material is markedly reduced.

Certain conditions existing in the bowel appear to modify the action of succinylsulfathiazole in the bowel. It has been observed that excessive diarrhea or extreme constipation with hard bulky stools interferes with the action of the drug. Liquid petrolatum in the bowel definitely reduces the efficacy of the compound. If the specimens of feces are incubated or left at room temperature, even though the feces are intimately mixed with the drug, the bacterial count of some of the specimens mounts rapidly. In searching for an explanation of the favorable influence of these rather widely different conditions on the growth of bacteria or, rather, of their inhibition of the bacteriostatic activity of succinylsulfathiazole, the following hypothesis can be put forth: If under normal conditions the bowel absorbs paraaminobenzoic acid-like split products, which act as inhibitors, from the stools, which have become semifluid as a result of the administration of the drug, this fact would explain the inhibition of the action of the drug in the four conditions cited: (1) diarrhea—the bowel mucosa does not favor absorption but rather favors excretion of fluid into the lumen; (2) constipation—the material within the inspissated feces does not come in contact with the absorbing surface; (3) liquid petrolatum—the fecal material does not come into intimate contact with the absorbing mucosa; (4) expelled feces—the split products accumulate and inhibit the action of the drug.

Action in the Presence of Ulcerating Lesions of the Gastrointestinal Tract.—While the results of the treatment of human beings with ulcerating lesions of various types will be the subject of a subsequent communication, it is appropriate here to discuss the antibacterial activity of succinylsulfathiazole in the presence of ulcerating lesions of the bowel. If the lesion is extensive, there seems to be a slight delay in the rate at which the bacterial flora is decreased, and on an average the count remains somewhat higher than that observed when the mucosa of the bowel is intact. This phenomenon may necessitate a larger dose of the drug to effect the desired result. There is no evidence that the presence of such lesions in the bowel appreciably alters the absorbability of the drug.

COMMENT

A series of derivatives of sulfanilamide which contain a free carboxyl group has been studied. The primary aromatic amino group has been condensed with a carboxyl group to form a substituted acid amide. This condensation alters their absorbability from the gastrointestinal tract. Furthermore, the carboxyl group probably influences the absorption and excretion of this series of drugs by the liver. The property causing the high biliary excretion might well influence the action in the upper gastrointestinal tract.

The use of succinylsulfathiazole as an intestinal antiseptic has met with excellent results even in the presence of ulcerating lesions of the bowel. At present one can say definitely that the bacterial flora of the gastrointestinal tract is significantly altered by the administration of succinylsulfathiazole, that the drug does not reach high concentrations in the blood, that approximately 5 per cent of the therapeutic oral dose is excreted by the kidneys and that the toxicity of the drug is relatively low. What may be the final clinical advantage to be derived from the lowering of the bacterial count or the interfering with the normal metabolic processes of the bacteria in the gastrointestinal tract before operation remains to be seen after extensive clinical trial and will be the subject of a subsequent communication. Likewise, the results of the use of this drug in the treatment of typhoid fever and bacillary dysentery will be reported later.

Because of the profound alterations in the physical form of the stools and the bacterial flora of the gastrointestinal tract, the effect of the administration of succinylsulfathiazole in the treatment of conditions resulting from chronic intestinal indigestion is worthy of investigation. The cholera vibrio, which is gram-negative and sensitive to an acid environment, might be expected to be vulnerable to the effects of this compound.

Any patient receiving this drug should be under close daily observation for toxic manifestations. The concentration of the drug in the blood and the total urinary output of the drug should be determined. So long as severe toxic reactions due to the administration of this drug are not encountered, its use will be extended.

SUMMARY

Sulfanilamide, derivatives of sulfanilamide and combinations of these compounds have been investigated by oral administration to dogs at four hour intervals. A series of these drugs condensed with dibasic acids to form substituted acid amides has been studied.

Succinylsulfanilamide and succinylsulfathiazole have high bacteriostatic activity as indicated by the effect on the coliform organisms in the gastrointestinal tract of the dog. These compounds have relatively strong acid properties, liberating carbon dioxide from aqueous solutions of inorganic carbonates and bicarbonates.

Succinylsulfathiazole is relatively resistant to chemical hydrolysis. It is split by bacteria to yield sulfathiazole. In vitro it has low bacteriostatic activity against *B. coli* in synthetic mediums. It is poorly absorbed from the gastrointestinal tract of man. A high concentration of succinylsulfathiazole can be maintained in the gastrointestinal tract of man without causing untoward toxic reactions. It has a high bacteriostatic action in the gastrointestinal tract of man as measured by the

inhibition of the coliform flora of the bowel. The administration of succinylsulfathiazole causes profound changes in the stools. They become semifluid and are rendered relatively odorless. The drug is rapidly excreted by the kidneys. The concentration of the drug in the blood remains low when administered orally. No crystals of the drug have been observed in the urine. The drug administered to human beings has not caused severe toxic reactions. It is excreted by the liver. Succinylsulfathiazole is split by its passage through both man and dog to yield sulfathiazole. The liver appears to be the site where hydrolysis occurs.

A preliminary working dosage of succinylsulfathiazole for man is given. Significant lowering of the coliform organisms in the bowel occurs in over 90 per cent of instances after the administration of succinylsulfathiazole in adequate doses. This drug is effective in the presence of extensive ulcerative lesions of the bowel. The administration of succinylsulfathiazole is suggested for the preoperative preparation of patients requiring operative procedures on the gastrointestinal tract and for the treatment of acute intestinal infections, such as typhoid fever and dysentery. The action of this drug is limited essentially to its local effect on the contents of the gastrointestinal tract.

Dr. J. Howard Brown gave assistance in the bacteriologic studies. Dr. Warfield M. Firor gave encouragement, support and constructive criticism. Sharp and Dohme provided most of the compounds used in this study.

CLINICAL USE OF SUCCINYLSULFATHIAZOLE

EDGAR J. POTH, M.D., PH.D.

AND

F. LOUIS KNOTTS, M.D.

BALTIMORE

The experimental basis for the use of succinylsulfathiazole as an agent for altering the flora of the gastrointestinal tract is presented in other papers by us.¹ In those communications the contents of the gastrointestinal tract were described as being profoundly altered by the oral administration of succinylsulfathiazole to experimental animals and man. Such a modification of the intestinal flora suggests the use of this drug especially in the preoperative preparation of the large bowel.

Succinylsulfathiazole has been given to 100 human beings without severe untoward reactions which could definitely be ascribed to its administration. The 100 patients receiving succinylsulfathiazole may be grouped as indicated in table 1.

The knowledge gained from an intensive study of the cases of these patients as it pertains to surgical procedures is the basis for this communication.

LOCAL BACTERIOSTATIC ACTION OF SUCCINYLSULFATHIAZOLE

Succinylsulfathiazole is so poorly absorbed from the gastrointestinal tract that only an average of 5 per cent of the ingested drug is excreted by the kidneys. Its action after oral administration, therefore, is essentially restricted locally to the contents of the bowel. The feces, which contain a moderate amount of mucus, become small in bulk, semifluid and relatively odorless. Ordinarily there will be two to four stools daily without hyperperistalsis or griping pain. Rarely does true diarrhea occur. The bacterial flora is profoundly altered; this is indicated by the effect on the coliform organisms. While the change in the coliform flora is used as an indicator of drug effect, it must be realized that all

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From the Department of Surgery, Johns Hopkins University School of Medicine.

1. (a) Poth, E. J., and Knotts, F. L.: Succinyl Sulfathiazole, a New Bacteriostatic Agent Locally Active in the Gastro-Intestinal Tract, *Proc. Soc. Exper. Biol. & Med.* 48:129, 1941. (b) Poth, E. J.; Knotts, F. L.; Lee, J. T., and Inui, F.: Bacteriostatic Properties of Sulfanilamide and Some of Its Derivatives: I. Succinylsulfathiazole, a New Chemotherapeutic Agent Locally Active in the Gastrointestinal Tract, *Arch. Surg.*, this issue, p. 187.

organisms in the bowel more susceptible than *Bacillus coli* to the antibacterial action of succinylsulfathiazole are even more profoundly affected. The Shiga, Flexner and Sonne strains of the dysentery bacillus are especially susceptible to the antibacterial action of this compound. The drug has no apparent effect on the growth of the typhoid and paratyphoid organisms, alpha *Streptococcus faecalis* or *Bacillus proteus*. *Bacillus aerobacter aerogenes* is more resistant than *B. coli* to the action of succinylsulfathiazole. The change in the character of the stools, including the disappearance of the fecal odor, suggests strongly that the growth of anaerobic proteolytic bacteria is particularly inhibited. A more exhaustive study of the bacteria retarded by this drug is being conducted and will be the subject of a subsequent communication.

TABLE 1.—*Patients Grouped According to Condition*

Group	Condition	Patients
1	Convalescent, with normal intact intestinal mucosa.....	15
2	Typhoid fever	12
3	Bacillary dysentery	19
4	Diarrhea (nonspecific)	14
5	Carcinoma of the right colon.....	4
6	Carcinoma of the left colon	15
7	Carcinoma of the transverse colon.....	2
8	Fecal fistulas involving the colon.....	3
9	Fecal fistulas involving the small bowel.....	3
10	Chronic ulcerative colitis	10
11	Diverticulitis	3
Total.....		100

MECHANISM OF ACTION

Accurate knowledge of the mode of action of sulfanilamide and its derivatives is as yet lacking. Theoretically, paraaminobenzoic acid or some chemically similar compound combines with a hypothetical substance, possibly an enzyme, to form a metabolite essential to the normal growth processes of certain bacteria. For the sake of simplicity we shall refer to this hypothetical substance as X. It is not known whether X is an endogenous or an exogenous substance as regards the bacterial cells. Fleming² showed that dead bacteria added to mediums interfered with the action of sulfanilamide. It is not inconceivable that X may be formed principally by certain strains of bacteria and that it may even be a factor in the phenomenon of symbiosis.

The mechanism and the competitive nature of the reactions of sulfanilamide and its derivatives and paraaminobenzoic acid have been

2. Fleming, A.: Observations on the Bacteriostatic Action of Sulfanilamide and M. & B. 693 and on the Influence Thereon of Bacteria and Peptone, *J. Path. & Bact.* 50:69, 1940.

discussed by Woods,³ Fildes,⁴ Lockwood⁵ and Wyss.⁶ The present concept is that sulfanilamide and its derivatives act because of their tendency to combine with substance X to form a conjugated compound unsuited to the metabolism of bacteria. From this concept it becomes obvious that X is rendered suitable for further metabolic processes depending on whether it is coupled with sulfanilamide or one of its derivatives as expressed by equation 1 or with paraaminobenzoic acid as indicated in equation 2.

Sulfanilamide or one of its derivatives + substance X \rightarrow Inactive substance (1)

Paraaminobenzoic acid + substance X \rightarrow Metabolic enzyme or metabolite (2)

The coupling agents will be determined by the concentrations of the competing reactants as governed by the law of mass action and the affinities or natural tendencies of the respective reactions to occur. Thus it is evident that the effectiveness of sulfanilamide or one of its derivatives will be influenced in any given instance not only by the concentration of the drug itself but also by the concentrations of the inhibiting agents and substance X.

Bacteriostasis will be realized in that thermodynamic environment which opposes the formation of the metabolic enzyme or the metabolite necessary for the multiplication of bacteria.

These concepts are particularly interesting with regard to the local bacteriostatic action of succinylsulfathiazole in the bowel. Because of the small bulk and the semifluid character of the feces, the contents of the bowel come into frequent and close contact with the absorbing mucosa. Since it is likely that paraaminobenzoic acid, similar split products and substance X are readily absorbed from the bowel, it can be assumed that the concentrations of these substances, which would favor the formation of the metabolic enzyme, will tend to be lowered and that thus the interaction of sulfanilamide or one of its derivatives and substance X to form a compound unsuitable for enzymatic utilization by the bacteria will be unopposed.

Further understanding of the mode of action of succinylsulfathiazole in the bowel might be forthcoming from an examination of certain conditions unfavorable to the action of the drug.

3. Woods, D. D.: The Relation of *p*-Aminobenzoic Acid to the Mechanism of the Action of Sulphanilamide, *Brit. J. Exper. Path.* **21**:74, 1940.

4. Fildes, P.: A Rational Approach to Research in Chemotherapy, *Lancet* **1**:955, 1940.

5. Lockwood, J. S.: Sulfanilamide and Its Derivatives in Surgical Infections: I. The Mode of Chemotherapeutic Action of the Sulfanilamides, *Surgery* **10**:493, 1941.

6. Wyss, O.: The Nature of Sulfanilamide Inhibition, *Proc. Soc. Exper. Biol. & Med.* **48**:122, 1941.

The following facts have been observed:

1. Liquid petrolatum interferes with the antibacterial activity of succinylsulfathiazole.

2. Watery diarrhea due to irritation of the mucosa strongly inhibits the antibacterial action of the drug.

3. Hard constipated stools which do not become semifluid after the administration of succinylsulfathiazole show only a partial lowering of the number of susceptible organisms.

4. On incubation at 37 C., the coliform organisms may multiply rapidly in some specimens of feces intimately mixed with succinylsulfathiazole.

5. The presence of extensive ulcerative lesions of the intestinal tract retards the rate at which the coliform organisms disappear under therapy, and the final level of the coliform population probably remains somewhat higher than in those instances in which the mucosa of the bowel is intact.

In the attempt to explain these rather diverse conditions which are unfavorable to the action of the drug, one might infer that an accumulation of paraaminobenzoic acid or a like substance in the feces reacts with substance X in these adverse circumstances and forms a metabolite suitable for normal metabolic processes of certain bacteria. Watery diarrhea due to irritation of the mucous membrane and the presence of extensive ulcerative lesions of the intestinal tract furnish a poor absorbing surface, and probably in these conditions additional inhibiting substances pour out. Hard, inspissated fecal material, as well as feces admixed and coated with liquid petrolatum, provides a poor surface for intimate contact with the absorbing mucous membrane of the bowel. Those stool specimens which favor the accumulation of inhibitors will allow bacterial proliferation in the presence of active drugs. It is freely admitted that this discussion is entirely speculative since we know of no facts to support or disprove this hypothesis.

As specifically applied to succinylsulfathiazole, these speculations must include a further consideration. Succinylsulfathiazole, as shown by Dr. W. Barry Wood, has practically no *in vitro* activity. It is therefore likely that succinylsulfathiazole must itself be converted to a more active compound, probably sulfathiazole. The addition of the succinyl radical to sulfathiazole renders it poorly absorbable from the bowel. The free carboxyl group gives succinylsulfathiazole relatively strong acid properties and by salt formation maintains a high ionic concentration of the drug admixed with the intestinal contents. Succinylsulfathiazole, therefore, may be strongly absorbed or adsorbed by the bacterial cells and may be hydrolyzed to give a high local concentration of a reactive, excited form of nascent sulfathiazole in intimate contact with the organism.

It has been observed that freshly voided feces contain only relatively small amounts of sulfathiazole but that after they stand at 37 C., the succinylsulfathiazole is slowly and progressively hydrolyzed to give free sulfathiazole (table 2). Although the amount of free sulfathiazole present in freshly voided feces is small as compared to the amount of succinylsulfathiazole, the concentration of the free sulfathiazole may vary ordinarily from 50 to 200 mg. per hundred cubic centimeters. Such concentrations of sulfathiazole should be sufficient to have strong bacteriostatic activity without any special assumptions as to the excited state of the sulfathiazole molecule.

METHOD OF INVESTIGATION

Each case was studied exhaustively for hemocytologic changes, for accumulation of the drugs in the blood, for the total urinary excretion

TABLE 2.—*Hydrolysis of Succinylsulfathiazole in Feces and in the Aqueous Solution of the Sodium Salt**

Days in Incubator at 37 C.	Molecular Concentration and Ratio of Sulfathiazole and Succinylsulfathiazole					
	In Incubated Stool Specimen			In Incubated Solution of Sodium Salt of Succinylsulfathiazole		
	Free (mM per L.)	Conjugated (mM per L.)	Ratio: Conjugated-Free	Free (mM per L.)	Conjugated (mM per L.)	Ratio: Conjugated-Free
0	2.55	65.2	25.6	34.6	550	15.9
4	8.05	59.1	7.4	30.7	510	16.6
13	9.8	54.9	5.6	34.8	635	18.2
34	13.3	40.4	3.0	40.35	624	15.2
41	16.5	40.0	2.4	46.4	660	14.2
48	16.85	50.0	2.9	39.6	663	16.7
63	16.5	55.0	3.3	34.4	507	14.7

* Within the rather wide limits of the accuracy of the analytic procedure a freshly expelled stool specimen contains only relatively small quantities of sulfathiazole. At 37 C. succinylsulfathiazole in contact with fecal material undergoes hydrolysis. This may be due to action of bacteria or ferments. The aqueous solution of succinylsulfathiazole sodium is relatively stable.

of the drug and for alterations of the intestinal flora as indicated by quantitative determinations of the coliform bacteria.

Since succinylsulfathiazole is partially hydrolyzed in the bowel and by the tissue cells, the blood will contain sulfathiazole, acetylsulfathiazole and succinylsulfathiazole.

A detailed description of the methods used in this study is given in our other article in this issue.^{1b}

PREOPERATIVE PREPARATION

Patients requiring surgical procedures on the intestinal tract receive a low residue diet, no liquid petrolatum and a minimum of cathartics and enemas. As previously stated, watery diarrhea retards the action of succinylsulfathiazole and must be avoided.

An initial oral dose of 0.25 Gm. of succinylsulfathiazole per kilogram of body weight is followed by a maintenance dose of 0.25 Gm. per kilogram daily, divided into six equal portions and given at four hour intervals. Since the bacterial count in the bowel mounts rapidly immediately on withdrawal of the drug, cleansing enemas should not be administered during the forty-eight hour period preceding operation.

The drug must be brought into direct contact with all portions of the bowel to effect an alteration of the bacterial flora. In the presence of enterostomies diverting the fecal stream or excluding various segments of bowel, the drug must be introduced directly into such segments by the most appropriate means.

All urine is saved for analysis. All stools are examined for consistency and odor, and daily bacteriologic counts are made. The coliform bacteria will usually fall from 10,000,000 to less than 1,000 organisms per gram of wet stool in one to seven days. Usually a satisfactory drop is obtained in three to five days. By this time the bowel will have become empty and the feces relatively odorless, and the patient will have been properly prepared for surgical procedures on the large intestine.

THE BOWEL AT OPERATION

When the abdomen of a patient who has been prepared with succinylsulfathiazole is opened, the bowel is found to be collapsed. The intestinal tract is free from gas and fecal material. The mucosa shows no evidence of local irritation due to action of the drug. If necessary, operation can be performed on the open colon without undue fear of peritonitis or local abscess formation.

The protection which is conferred by the action of this drug is illustrated by the following experimental observation. If at laparotomy the bowel of a dog which has received satisfactory succinylsulfathiazole therapy is found to be empty, the descending colon can be divided transversely through one third of its diameter and the abdomen closed with the lesion ordinarily healing without the production of fatal peritonitis.

POSTOPERATIVE ADMINISTRATION OF SUCCINYLSULFATHIAZOLE

Administration of succinylsulfathiazole, in amounts equal to the pre-operative dose, is resumed after operation as soon as the patient can take an ounce (28 Gm.) of warm water without undue nausea. Although the patient may be required to take six large (0.5 Gm.) tablets of drug every four hours, it is surprising that nausea and vomiting seldom occur.

The postoperative course is smooth. There is little distention, and gas pains are strikingly diminished. Occasional superficial wound infection has occurred after extensive operations on the large bowel, but deep abscesses and peritonitis have not been encountered.

TABLE 3.—*Dosage of Succinylsulfathiazole with the Concentration of the Drug in the Blood and the Feces and the Quantity of the Drug Excreted in the Urine in Cases in Which the Gastrointestinal Tract Exhibited Various Lesions*

Patient and Weight, Kg.	Day	Dally Dose, Gm.; Divided Into Six Equal Doses	Concen- tration of the Drug in the Blood, Mg. per 100 Cc.		Dally Urinary Output, Gm.		Con- centration of the Drug in the Stools, per Cent	Comment
			Free	Conju- gated	Free	Conju- gated		
M. N. 56	1	28	0.07	0.07	Large ulcerating carcinoma of rectum; B. coli count dropped from 10 ⁹ to 10 ³ ; operation done after only 3 days of treatment with drug; postoperative course uneventful; no distention, nausea or vomiting; no toxic symptoms; 8.2% of ingested drug excreted in urine
	2	28	1.3	5.6	0.34	0.40	7.5	
	3	14	0.8	1.2	0.33	0.58	5.1	
	4	..	0.81	1.0				
	5	14	1.17	1.2	0.50	0.49		
	6	14	1.30	1.0	0.47	0.70		
	7	14	1.30	1.0	0.37	0.82		
	8	9	1.30	1.2	0.41	0.97	8.0	
	9	0.22	0.62	6.0	
	10	0.13	0.45		
	11	0.06	0.15		
	12	0.06	0.18		
P. R. 70	1	24	0.24	0.25	Ulcerating carcinoma of rectum; coli- form organisms dropped from 10 ⁹ to 10 ³ in 4 days and remained at this level; operation on ninth day; no postopera- tive complications; no distention; no gas pains after abdominal perineal resection; no toxic manifestations; 6.85% of ingested drug excreted in urine
	2	18	1.08	2.50	0.47	1.57		
	3	18	1.50	4.70	0.30	0.70		
	4	18	0.80	0.80	0.23	0.46	5.7	
	5	18	1.30	0.20	0.24	0.42	4.8	
	6	18	0.80	3.4	0.54	1.00	4.6	
	7	18	1.00	3.00	0.20	0.40	4.9	
	8	18	1.30	0.80	0.35	0.35	10.5	
	9	12	1.30	2.30	0.04	0.04		
	10	6	1.20	0.00	0.35	0.22		
	11	18	0.80	1.20	0.78	0.34		
	12	6	0.80	2.80	0.60	0.02	3.5	
	13	..	0.75	0.10	0.50	0.57	4.5	
	14	..	1.00	0.33	0.02	0.00		
	15	..	1.2	0.60	0.03	0.00		
	16	..	0.20	0.00	0.00	0.00		
M. E. 75	1	25	Partial obstruction in sigmoid on basis of old diverticulitis; drug given 5 days before operation; bowel wall much thickened and scarred with numerous small sinuses and diverticula; few small sessile polypi present; some soiling at time of operation; postoperative course uncomplicated—no distention or gas pains; B. coli count dropped from 10 ⁸ to 60 organisms per Gm. of wet stool; although previously there had been a drug reaction with a rash after sulfa- thiazole therapy, there were no toxic manifestations due to administration of succinylsulfathiazole; 5.8% of ingested drug excreted in urine
	2	18	1.0	1.5	0.28	1.0		
	3	18	0.8	1.4	0.14	1.24		
	4	18	0.5	1.4	0.70	0.28	6.9	
	5	15	1.8	0.67	0.00		
	6	0	1.2	3.3	0.21	0.23	8.0	
	7	15	0.13	0.02		
	8	18	1.0	1.2	0.47	0.82		
	9	18	1.2	1.6	0.24	0.15		
	10	18	0.8	1.7	0.46	1.18		
	11	18	1.3	1.8	0.34	0.24		
	12	18	0.27	0.27		
	13	18	1.3	2.5	0.43	0.66	5.7	
	14	18	0.26	0.50		
	15	18	0.7	2.2	0.27	0.61		
	16	18	0.60	1.33	5.2	
	17	0.26	0.64		
	18	..	0.8	1.7	0.10	0.26	4.4	
	19	0.10	0.23	1.2	
	20	..	0.1	0.4	0	0.10		
B. D. 55	1	30	Operation several months previously for abscess resulting from perforation of descending colon by fish bone; fecal fistula resulted; actinomycosis found on one examination; attempt made to close fistula without success; sulfathia- zole therapy did not prevent extensive breakdown of wound resulting in forma- tion of double-barreled colostomy; 3 mo. later succinylsulfathiazole given (0.25 Gm. per Kg. by mouth and 0.25 Gm. per Kg. in distal limb of colostomy daily); because of involvement of soft tissues sulfathiazole was given begin- ning on 9th day to saturate general body tissues; colostomy closed on 13th day; sulfathiazole discontinued on 26th day; after operation 0.25 Gm. per Kg. daily of succinylsulfathiazole given by mouth; postoperative course unevent- ful; no toxic manifestations; coliform count dropped from 10 ⁸ to 0
	2	27	0.6	1.4	0.19	0.36	4.2	
	3	27	0.7	1.5	0.14	0.22	6.5	
	4	27	0.27	0.28	8.1	
	5	27	1.3	1.6	0.09	0.20		
	6	27	0.8	1.4	0.10	0.22		
	7	27	0.4	1.0	0.28	0.28	8.3	
	8	27	0.3	2.2	0.40	0.01	6.6	
	9	27	1.8	2.3	0.16	0.10	4.2	
	10	27	1.4	5.5	
	11	27		
	12	22.5	5.3	0.8	1.6	
	13	0	2.4	4.4	4.9	
	14	11		
	15	13.5	7.2	1.2		
	16	13.5	1.4	
	17	13.5	5.4	2.4	3.4	
	18	13.5		
	19	13.5	4.0	4.8	
	20	13.5	5.4	
	21	13.5	5.3	
	22	13.5	4.4	1.7		
	23	13.5		
	24	13.5	4.9	0.8		
	25	13.5		
	26	13.5	5.9	0.4		
	27	13.5		
	28	13.5	0.9	1.0		
	29	13.5		
	30	13.5		
	31	13.5		

TABLE 3.—Continued

Patient and Weight, Kg.	Day	Daily Dose, Gm.; Divided Into Six Equal Doses	Concentration of the Drug in the Blood, Mg. per 100 Cc.		Daily Urinary Output, Gm.		Concentration of the Drug in the Stools, per Cent	Comment
			Free	Conjugated	Free	Conjugated		
L. N. 27	1	13.7	0.9	1.5	0.28	0.30	Boy 10 yr. old with kidney stone, ileostomy and extensive prolapse of ileostomy; operative treatment shown in fig. 1D; coliform organisms dropped from 10^{10} to less than 10 ; uneventful postoperative course; no toxic drug reaction; 6% of ingested drug excreted in urine
	2	7.5	0.07	0.01		
	3	7.5	0.7	0.8	0.22	0.03		
	4	7.5	0.20	0.42		
	5	7.5	0.17	0.02		
	6	7.5	0.37	0.61		
	7	7.5	1.7	1.0	0.33	0.86		
	8	7.5	0.27	0.58		
	9	7.5	1.6	1.6	0.10	0.12		
	10	7.5	0.08	0.25		
	11	7.5	1.4	3.0	0.08	0.26		
	12*	0.09	0.17		
	13	7.5	0.08	0.14		
	14	7.5	0.21	0.28		
	15	7.5	0.38	0.93		
	16	7.5	0.17	0.31		
	17	7.5	0.9	2.5	0.17	0.41		
	18	7.5	0.18	0.43		
	19	7.5	0.16	0.19		
	20	7.5	0.06	0.04		
	21	7.5	0.11	0.09		
	22	1.3	0.4	0.2	0.22	0.22		
T. S. 52	1	21	1.4	1.2	0.01	0.24	Woman 49 yr. old with rectal bleeding for 2 mo.; polypoid adenocarcinoma of sigmoid; coliform count dropped from 10^7 to less than 10 ; open resection of sigmoid with end to end suture; postoperative course uneventful as regards gastrointestinal tract; sustained radial palsy during operation; after operation sulfathiazole given for pulmonary complication; drug reaction with kidney damage; prior to sulfathiazole therapy 3.8% of ingested succinylsulfathiazole excreted in urine; high blood levels from 19th day due to administration of sulfathiazole
	2	13	0.4	1.9	0.17	0.16		
	3	12	0.31	0.51		
	4	12	1.0	1.4	0.20	0.23		
	5	12	0.15	0.30		
	6	12	1.1	1.6	0.14	0.16		
	7	12	0.7	0	0.15	0.20		
	8	12	0.19	0.21		
	9	12	0.19	0.11		
	10	12	0.16	0.05		
	11	8	0.9	0.3	0.17	0		
	12	12	0.4	1.6	0.52	0.50		
	13	12	0.5	1.3	0.18	0.23		
	14	12	0.16	0.03		
	15	12	0.24	0.24		
	16	12	0.15	0.30		
	17	12	0.05	0.07		
	18*		
	19	..	3.5	5.3	1.06	0.45		
	20	12	8.3	2.5	3.95	2.41		
	21	12	2.90	1.40		
	22	12	5.8	3.6		
	23	12		
	24	12	2.66	2.05		
	25	12	1.47	0.93		
	26	12	1.86	2.07		
	27	12		
	28	12		
	29	12	1.06	1.64		
	30	6	6.8	1.6	0.74	0.38		
E. A. 72	1	33	Filipino man 43 yr. old with long history of pain in right lower quadrant of abdomen; exacerbation for past 3 weeks with palpable mass in right lower quadrant of abdomen; operation delayed because of question regarding diagnosis; tumor of cecum found at operation; resection of colon on right side to midtransverse with open ileocolostomy; postoperative course uneventful; dismissed on 17th postoperative day; coliform count dropped to 600; no toxic drug reactions; 4.1% of ingested drug excreted in urine
	2	18		
	3	18		
	4	18	0.86	2.64		
	5	18		
	6	18		
	7	18		
	8	18	0.86	2.53		
	9	18		
	10*	2.19†	1.78†		
	11	5	0.055	0.058		
	12	15	0.059	0.043		
	13	15.5	0.60	0.445		
	14	18	1.29	0.18	0.91	0.62		
	15	18	0.236	0.416		
	16	18	0.14	0.23		
	17	18	0.29	0.40		
	18	18	0.33	0.35		
	19	18	0.29	0.42		
	20	18	0.22	0.35		
	21	18	0.32	2.06	0.27	0.33		
	22	18	0.29	0.37		

* Day of operation.

† Total preoperative urinary excretion.

TABLE 3.—Continued

Patient and Weight, Kg.	Day	Daily Dose, Gm., Divided Into Six Equal Doses	Concentration of the Drug in the Blood, Mg. per 100 Cc.		Daily Urinary Output, Gm.		Concentration of the Drug in the Stools, per Cent	Comment
			Free	Conjugated	Free	Conjugated		
L. E. 48	1	24	Woman 57 yr. old with fecal fistula after resection of cecum for carcinoma 6 years before present admission; coliform count dropped from 10^6 to less than 10^3 ; operative procedure shown in fig. 10; superficial wound infection and alpha Str. faecalis cystitis after operation; postoperative course otherwise uneventful; dismissed on 22d day after operation; no toxic reaction to drug; 6.4% of ingested drug excreted in urine
	2	12	0.86	8.12	
	3	12	
	4	12	
	5	12	
	6	12	
	7	12	
	8	12	
	9	12	
	10	12	
	11	12	
	12*	2.54†	7.15†	
	13	6	0.16	0.033	
	14	12	1.73	0.72	
	15	12	
	16	12	
	17	12	
	18	12	0.251	0.366	
	19	12	0.094	0.122	
	20	12	0.062	0.076	
	21	12	
	22	12	0.43	1.55	0.128	0.156	
	23	12	
	24	0.064	0.142	
H. S. 45.4	1	4	Negro woman 63 yr. old with severe diarrhea and large amounts of blood in stools; hemoglobin content, 20%; carcinoma of hepatic flexure; repeated transfusions; coliform count did not drop until diarrhea was controlled with lead and opium; count then dropped immediately from 10^6 to 700; resection of colon on right side with ileotransversostomy; postoperative course uncomplicated; no toxic drug reaction; dismissed on 20th postoperative day; 2.4% of ingested drug excreted in urine; hemoglobin content, 80%
	2	12	0.000	0.025	
	3	12	0.128	0.354	
	4	12	0.010	0.023	
	5	12	0.113	0.272	
	6	12	0.062	0.176	
	7	12	
	8	15	0.86	2.68	0.035	0.094	
	9	18	0.092	0.193	
	10	18	0.036	0.082	
	11	18	
	12	18	
	13	18	
	14	18	
	15	18	0.039	0.145	
	16	12	
	17*	0.115	0.326	
	18	12	
	19	18	0.101	0.224	
	20	18	
	21	18	0.118	0.171	
	22	18	0.047	0.146	
	23	18	0.036	0.046	
	24	18	0.035	0.058	
	25	18	0.088	0.080	
	26	18	0.197	0.302	
	27	0.065	0.119	
	28	0.294	0.336	
G. R.	1	15	0.103	0.231	Woman 33 yr. old with multiple fecal fistulas; five previous abdominal operations, including colectomy and ileosigmoidostomy; coliform organisms dropped from 10^7 to 10^3 ; extensive operation with open end to side anastomosis of bowel in presence of a massive adhesion; course uncomplicated; all fistulas closed; no toxic drug reaction; 3.7% of ingested drug excreted in urine; dismissed on 22d postoperative day
	2	15	0.255	0.796	
	3	15	0.43	1.42	0.168	0.536	
	4	15	0.104	0.294	
	5	15	0.309	0.556	
	6	15	0.202	0.493	
	7	15	
	8	19	1.08	0.86	0.176	0.300	
	9	27	0.316	0.845	
	10	27	0.257	0.655	
	11	27	1.08	2.12	0.306	0.977	
	12	27	0.212	0.590	
	13	27	0.202	0.501	
	14	27	0.426	0.644	
	15	27	0.145	0.614	
	16*	15	0.234	0.938	
	17	5	0.072	0.223	
	18	15	0.044	0.108	
	19	15	0.310	0.325	
	20	15	0.172	0.185	
	21	15	0.172	1.242	
	22	15	1.38	2.84	0.530	0.596	
	23	15	0.128	0.255	
	24	15	0.119	0.180	
	25	15	0.127	0.133	
	26	15	0.026	0.026	
	27	15	0.084	0.023	
	28	15	0.050	0.113	
	29	0.062	0.041	
	30	0.034	0.082	
	31	0.009	0.026	
	32	0.024	0.000	
	33	..	0.43	0.74	
	34	0.004	0.000	

* Day of operation.

† Total preoperative urinary excretion.

While the action of succinylsulfathiazole is largely restricted to its local effect on the contents of the gastrointestinal tract, other derivatives of sulfanilamide, especially sodium sulfathiazole administered intravenously, are not given except when extra-abdominal complications develop. Patients receiving only succinylsulfathiazole experience an unusually simple convalescence.

In the course of this study no additional derivatives of sulfanilamide have been placed in the peritoneal cavity or in the operative wound, because of the desire to study the effect of succinylsulfathiazole alone. Subsequently, in view of the apparent advantage of placing sulfanilamide or one of its derivatives in the abdominal cavity and the wound at the time of operation, this procedure might well be added to succinylsulfathiazole therapy. Again, it might be desirable in certain instances to saturate the general body tissues with one of the readily absorbed compounds of this group both before and after operation, and this procedure has, in fact, been carried out on 2 of the patients included in this study (table 3).

The period of postoperative therapy is determined by the condition observed at operation. After abdominoperineal resection for carcinoma of the rectosigmoid, the drug is given for approximately one week to allay distention. However, after colonic resection with primary suture, it is administered for twelve to fourteen days.

Again it should be emphasized that the drug should not be withheld after operation if it is at all possible for the patient to take water, because the bacterial flora is rapidly restored on withdrawal of the compound. It is not unusual for the coliform count to increase from 100 to 10,000,000 organisms per gram of wet stool within twenty-four hours after the discontinuance of therapy.

SUCCINYLSULFATHIAZOLE IN TREATMENT

In an attempt to present evidence of the apparent value of an agent which will modify the physical character and the bacterial count of the fecal material in the gastrointestinal tract before and after operations on the bowel, the pertinent data covering a few of the patients operated on and treated with succinylsulfathiazole are given in table 3.

The material presented in tabular form readily indicates the general type of patient treated. A detailed presentation of the case of L. N. (table 3) discloses a particularly interesting problem. A 10 year old boy was operated on for acute intestinal obstruction fourteen months before the hospitalization recorded in the table. Appendectomy had been performed twenty-two months before the appearance of acute obstructive symptoms. One week prior to the present admission roentgen study made after the finding of hematuria revealed a staghorn

stone of the right kidney. On admission, examination showed also a large segment of small bowel prolapsed through a right pararectus tangential enterostomy. Communication between the enterostomy, the colon and the rectum could not be demonstrated.

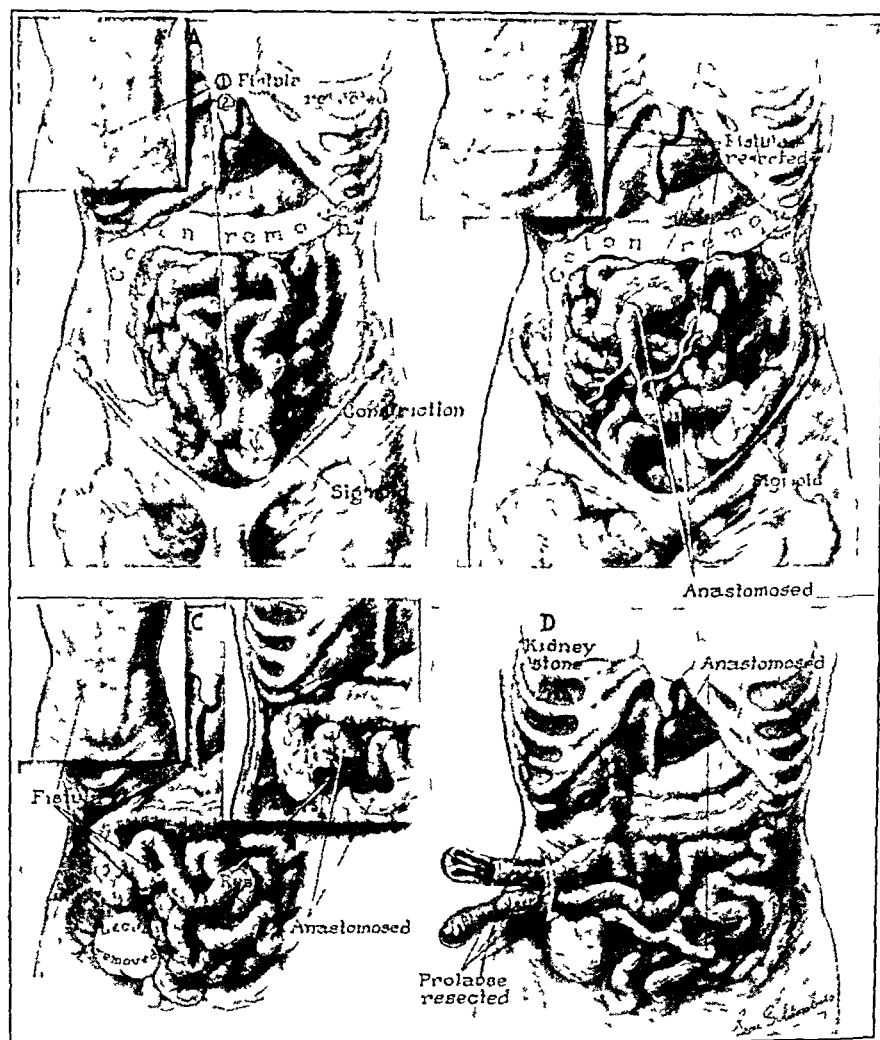


Figure 1

(See legend on opposite page)

Anticipating that operation might necessitate an extensive intra-abdominal procedure, we considered it desirable to lessen the virulence of the intestinal flora. The presence of a kidney stone should preclude any such attempt by the administration of sulfanilylguanidine, because we have shown that kidney stones composed of sulfanilylguanidine are formed in a high percentage of dogs receiving therapeutic doses of that drug. Since, however, Poth, Knotts, Lee and Inui^{1b} had demonstrated

that succinylsulfathiazole can be excreted in high concentration in the urine as a soluble salt, it was considered safe to administer succinylsulfathiazole in the presence of a stone in the kidney. The drug was given without evidence of any change in the urinary tract, and satisfactory surgical treatment was undertaken as indicated in figure 1 *D*.

EXPLANATION OF FIGURE 1

Pathologic conditions of the bowel presenting various problems in the administration of succinylsulfathiazole.

A. A fecal fistula developed after colectomy and ileosigmoidostomy for ulcerative colitis. The patient had received sulfanilylguanidine prior to operation; he returned to the hospital for closure of the fistula. Administration of succinylsulfathiazole failed to lower coliform organisms below 30,000 colonies per gram of wet stool. At operation a short constricted blind end of sigmoid was found to contain 1,000,000 *B. coli* per gram of fecal material. A culture from the proximal loop showed approximately 1,000 *B. coli* per gram of bowel contents. The drug was not entering the short blind end of sigmoid in sufficient quantity. Closure was effected with primary healing.

B. This patient had five surface fecal fistulas after five operations during the course of which colectomy was performed for chronic ulcerative colitis. No feces were passed per rectum. The patient received 0.25 Gm. of succinylsulfathiazole per kilogram daily in six oral doses and an equal amount of the drug per rectum administered in three daily instillations. Culture of the material obtained from both the fistulas and the rectum showed less than 1,000 *B. coli* per gram. At operation a maze of adhesions was encountered. In dissecting out the fistulas, two openings were made in the bowel. The maze of adhesions was unraveled by opening the blind stump of the sigmoid, introducing catheters into the three open ends of bowel and placing a fourth catheter into the rectum to demonstrate the course and continuity of the bowel. These catheters were handled without regard to the fact that they had been in contact with fecal material. Primary end to end suture was performed, the wound was closed with silk, and healing occurred by primary intention.

C. A fecal fistula occurred after resection of a carcinoma of the cecum six years previously. Feces were seldom passed per rectum. Succinylsulfathiazole was administered orally and per rectum in doses of 0.25 Gm. per kilogram daily by each route. After a satisfactory alteration of the intestinal flora, dissection of the fistulas, resection of a segment of bowel and end to end suture were done as indicated. The result was healing by primary intention.

D. A boy of 10 years entered the hospital in the condition shown. In the presence of a kidney stone, succinylsulfathiazole was given by mouth and introduced into the distal limb of the enterostomy. Obviously, the drug could not possibly be introduced into the distal atrophic blind segment of the ileum. Material from the proximal limb of the ileostomy contained less than 10 *B. coli* per gram. End to side anastomosis was performed as indicated. The postoperative course was distinguished by the occurrence of only moderate distention and transient gas pains. Damage resulting to the urinary tract from the growth of the kidney stone by the crystallization of the drug on the surface was not evident.

TOXIC MANIFESTATIONS

The administration of succinylsulfathiazole to patients with various lesions of the gastrointestinal tract presents no special problems. The degree of absorption is essentially the same and is not conditioned by the state of the bowel. The drug has been administered in the presence of partial obstruction without evident increase in the quantity of drug excreted in the urine. A series of patients from whom complete urinary collections were obtained for the entire period of therapy showed an average excretion by the kidneys of 4.85 per cent of the ingested compound. The concentration of the drug in the blood usually ranged from 0.5 to 1.0 mg. per hundred cubic centimeters for sulfathiazole and from 1.0 to 2.0 mg. for the conjugated sulfathiazoles. Toxicity is conditioned

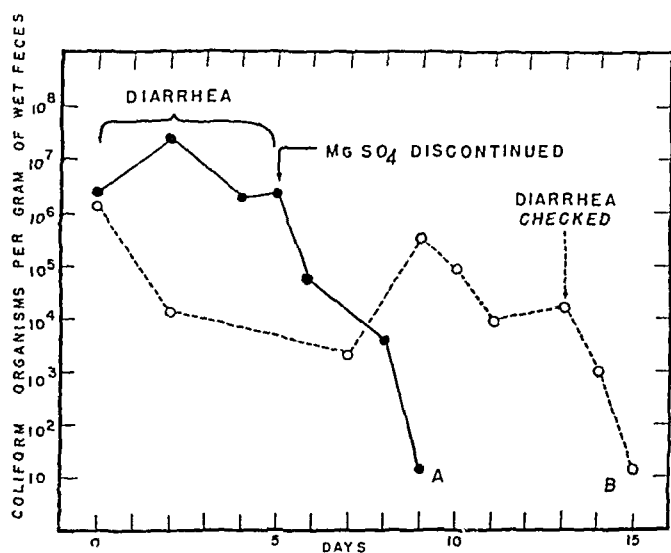


Fig. 2.—Retardation of the action of succinylsulfathiazole in the presence of watery diarrhea.

A. The patient received 0.25 Gm. per kilogram daily of succinylsulfathiazole divided into six equal doses for nine days. During the first five days this patient had watery diarrhea due to the administration of magnesium sulfate. The count of coliform organisms remained unchanged during this period. After discontinuance of administration of magnesium sulfate on the fifth day, the diarrhea stopped, and the intestinal flora was profoundly altered.

B. This patient had a large ulcerating lesion, diagnosed as carcinoma, at the hepatic flexure of the colon, accompanied by severe protracted hemorrhage and diarrhea. Succinylsulfathiazole (0.5 Gm. per kilogram daily) failed to alter satisfactorily the intestinal flora until the diarrhea was checked by the administration of lead and opium in the form of pills.

not merely by the concentration of a drug in the blood but also by the total quantity of the drug absorbed and disposed of by the body tissues. There were no hemocytologic changes.

Vomiting did not occur. Some patients complained of a loss of appetite, while others said that the appetite was improved. Three

patients had diarrhea. One of these patients had a massive hemorrhage from a large eroded carcinoma of the rectum. No rashes occurred. In patients with a rash from sulfathiazole this toxic manifestation did not again develop on the administration of succinylsulfathiazole, even though the sulfathiazole rash disappeared only a day before succinylsulfathiazole therapy was started. If, however, succinylsulfathiazole was given while the rash due to sulfathiazole was still present, clearing apparently did not occur. In summary, it can be stated that severe toxic manifestations due to the administration of succinylsulfathiazole were not observed. The drug was given continuously for periods of sixteen weeks without untoward effects.

FAILURES

Severe watery diarrhea, whatever the cause, is the most frequent cause of failure to lower the bacterial flora. Obviously, the remedy is to check the diarrhea (fig. 2). If the diarrhea cannot be stopped, it may not be possible to effect a significant alteration of the intestinal bacterial flora even with massive doses of succinylsulfathiazole.

In the presence of a blind loop of bowel the drug may not enter the segment in sufficient quantity for antibacterial effect. An attempt should be made by change of position to cause the drug to enter the isolated segment; otherwise a favorable result cannot be expected (fig. 1 *A*).

COMMENT

An intensive study of the first 100 patients to whom succinylsulfathiazole has been administered permits some rather definite impressions to be formed.

Certain conditions interfere with the action of the drug. If these can be eliminated, adequate administration of the compound always results in profound alteration of the physical properties and the bacterial flora of human feces. In 5 of the 100 cases included in this study satisfactory lowering of the coliform count was not realized; in 2 of these 5 cases there was severe, uncontrollable diarrhea; in 2 cases there were blind loops of bowel into which the drug did not enter, and in the fifth case there was intestinal indigestion so that the stools did not become semifluid during drug therapy. An occasional failure to alter the stools will no doubt occur, but success can be anticipated for about 95 per cent of all patients adequately treated.

In the bacteriologic investigation only the coliform organisms were studied quantitatively. *B. coli* was selected for quantitative study because of the ease with which its differentiation is possible on desoxycholate agar plates inoculated with such complicated bacterial mixtures as are present in feces. Because of the profound changes in the feces, it is likely that various organisms, including the anaerobic bacteria, are

affected. The shift in the count of *B. coli* may well be considered a convenient indicator.

While it is not desirable to draw hard and fast conclusions from such a limited clinical study, one is impressed by the smooth convalescence experienced by patients receiving preoperative and postoperative treatment with succinylsulfathiazole. Further, we present these observations and impressions with the full realization that much more experience must be gained before dogmatic statements can be made regarding the effectiveness of succinylsulfathiazole as an aid to surgical procedures. If after a minimum of five years of critical use this drug or another of similar properties has earned a place in the surgical armamentarium, the impressions and speculations presented here will have proved validity. The smooth, uncomplicated postoperative convalescence appears significant even at this time, and one is inclined to feel that some such regimen will prove to be an adjuvant to surgical procedures on the large bowel. It is not intended to imply that this is a signal to permit poor surgical performance or to relax rigid surgical asepsis. Rather it is hoped that a procedure of this kind may add another safeguard. Patients receiving succinylsulfathiazole should be closely observed with frequent determinations of the concentration of the compound in the blood and of the total urinary output of the drug.

One postoperative death has occurred. In this instance anuria developed after a Miles operation for carcinoma of the rectum. Postmortem examination showed that both ureters had been mechanically blocked by a large pack placed in the posterior wound of an abdominal perineal resection.

SUMMARY

Succinylsulfathiazole has been administered to 100 human beings.

Approximately 5 per cent of the succinylsulfathiazole administered orally in therapeutic dosage levels was excreted in the urine. A detailed report of the urinary excretion of the drug is given.

Succinylsulfathiazole can be maintained in high concentration in the diseased gastrointestinal tract of man with low concentrations of the drug in the blood and without the development of toxic manifestations.

A profound change in the physical characteristics and the bacterial flora of the feces can be expected in 95 per cent of all cases after adequate treatment with succinylsulfathiazole.

The possible mechanism of action of succinylsulfathiazole is discussed.

Observations on a series of patients treated with succinylsulfathiazole and operated on are reported.

Drs. Warfield M. Firor, Alfred Blalock, James M. Mason III and numerous other physicians and surgeons gave us help and allowed us to use their patients in this study.

SODIUM SULFADIAZINE IN THE TREATMENT OF EXPERIMENTAL STREPTOCOCCIC INFECTION

BARTON McSWAIN, M.D.

AND

FRANK GLENN, M.D.

NEW YORK

The purpose of this study is to determine the effect of large doses of sodium sulfadiazine (the monohydrate sodium salt of 2-[paraamino-benzenesulfonamido]-pyrimidine) given subcutaneously to rabbits with wounds inoculated with a measured amount of a culture of beta hemolytic streptococcus of known virulence.

METHOD

Rabbits weighing from 2,200 to 3,800 Gm. were used. Soluble pentobarbital (0.80 cc. of a solution containing 0.06 Gm. of pentobarbital per cubic centimeter) administered in an aural vein supplemented by light open drop ether was used to induce anesthesia for all operations. Aseptic technic was used throughout. A longitudinal incision 2 cm. long was made 1 cm. to the left of the midline posteriorly and 2 cm. inferior to the lowest rib. The skin, the subcutaneous tissue and the muscle sheath were incised. By means of a brass cork borer with a diameter of 1 cm., a segment of sacrospinalis muscle 2 cm. in depth was removed. The muscle was crushed with an artery forceps and replaced. The fascia was closed with interrupted sutures of fine silk and the skin with a continuous suture of fine silk. An identical procedure was performed on the right side except that a pledget of dry cotton 1 cm. square and approximately 2 mm. thick was placed in the wound before the muscle was inserted. A two layer thickness of gauze was placed over each incision; this was sealed with collodion.

EXPERIMENTS

Control Group 1 (Operation).—Two animals were operated on with the procedure just outlined. All four wounds healed by first intention. The animals were observed for two weeks after operation.

Control Group 2 (Inoculation).—Twelve animals were operated on in the manner described. A stock broth culture of beta hemolytic streptococcus was obtained from Dr. D. Murray Angevine.¹ This strain was termed by him NY 5.

From the Department of Surgery, New York Hospital and Cornell University Medical College.

1. Cecil, R. L.; Angevine, D. M., and Rothbard, S.: Experimental Arthritis in Rabbits Produced with Streptococci and Other Organisms, *Am. J. M. Sc.* **198**: 463-475, 1939.

It was originally isolated in a case of scarlet fever by Dr. Alphonse R. Dochez. Its virulence for rabbits was known. The culture used was eighteen hours old and contained 107,000,000 organisms per cubic centimeter; 0.10 cc. was implanted

TABLE 1.—*Blood Levels of Sodium Sulfadiazine Administered to Two Rabbits*

Rabbit 4		Rabbit 61	
Time	Sodium Sulfadiazine, Mg. per 100 Cc.	Time	Sodium Sulfadiazine, Mg. per 100 Cc.
10 a.m.	1.2	10 a.m.	2.8
11 a.m.	Trace	11 a.m.	1.8
2 p.m.	1.5	2 p.m.	3.8
4 p.m.	1.5	4 p.m.	1.2
8 p.m.	0.02	8 p.m.	2.1
12 midnight.....	Faint trace	12 midnight.....	Very faint trace
8 a.m.	Very faint trace	8 a.m.	Very faint trace

TABLE 2.—*Data on Duration of Life and Cultures of Rabbits in Control Group 2*

Rabbit	Duration of Life, Hr.	Blood Culture	Culture of Wound in Right Lumbar Region	Culture of Wound in Left Lumbar Region
46	26	Beta hemolytic streptococcus	Beta hemolytic streptococcus	Beta hemolytic streptococcus
69	16	Beta hemolytic streptococcus	Beta hemolytic streptococcus	Beta hemolytic streptococcus
70	16	Beta hemolytic streptococcus, Staphylococcus albus, gram-negative bacilli	Beta hemolytic streptococcus	Beta hemolytic streptococcus
73	16	Beta hemolytic streptococcus	Beta hemolytic streptococcus, gram-negative bacilli	Beta hemolytic streptococcus, gram-negative bacilli
76	20	Beta hemolytic streptococcus	Beta hemolytic streptococcus	Beta hemolytic streptococcus
77	23	Beta hemolytic streptococcus	Beta hemolytic streptococcus	Beta hemolytic streptococcus
80	16	Beta hemolytic streptococcus	Beta hemolytic streptococcus	Beta hemolytic streptococcus
81	80	Beta hemolytic streptococcus	Beta hemolytic streptococcus	Beta hemolytic streptococcus
83	Survived	No growth	Beta hemolytic streptococcus	Beta hemolytic streptococcus
84	18	Beta hemolytic streptococcus	Beta hemolytic streptococcus	Beta hemolytic streptococcus
88	18	Beta hemolytic streptococcus	Beta hemolytic streptococcus	Beta hemolytic streptococcus
91	108	Beta hemolytic streptococcus	Beta hemolytic streptococcus	Beta hemolytic streptococcus

into each incision before the muscle or the cotton was inserted. Except for the absence of the determination of sodium sulfadiazine in the blood, these animals were followed exactly in the manner to be described under "Crucial Experiment."

Control Group 3 (Administration of Sodium Sulfadiazine).—A 10 per cent solution of sodium sulfadiazine in distilled water was used. In the New York Hospital 0.10 Gm. per kilogram of body weight is used clinically as the daily dose; this amount was administered in three divided doses at 8 a. m., 12 noon and 4 p. m. to 2 rabbits. Blood was obtained at 10 a. m., 11 a. m., 2 p. m., 4 p. m., 8 p. m., 12 midnight and 8 a. m. The level of sodium sulfadiazine in the blood is shown in table 1.

As can be noted, this dosage failed to produce a satisfactory blood level. Hence, a total daily dose of 0.4 Gm. per kilogram of body weight was arbitrarily used. This was given in six divided doses at four hour intervals. The drug was administered subcutaneously in the costovertebral region several centimeters cephalad to the incision. The drug was given to 6 animals for seven days. Blood

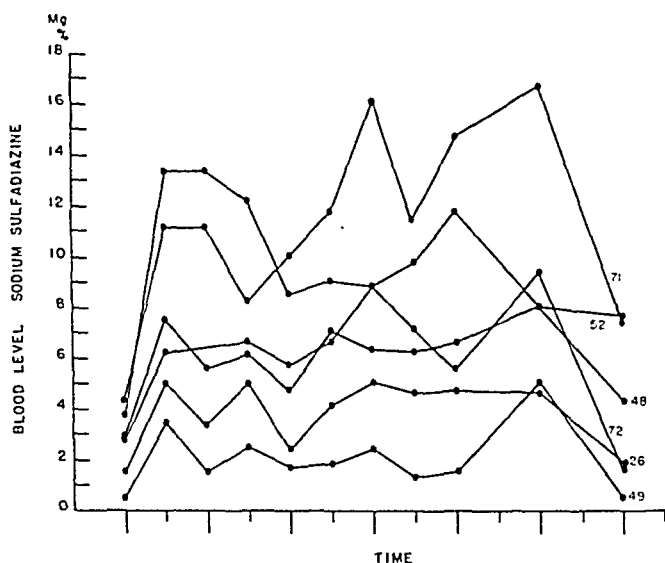


Chart 1.—Blood levels of sodium sulfadiazine for rabbits in control group 3. Time is indicated in twelve hour intervals.

was removed from an incised aural vein at twelve hour intervals for the first four days and twenty-four hour intervals for the last three days. No untoward reactions, either local or systemic, were noted in these animals, and all survived. The blood levels are shown in chart 1.

Clinical Experiment.—The crucial experiment was done on two series of 12 animals each. Twenty-four rabbits were operated on as described; 0.10 cc. of the previously mentioned culture was implanted into each wound. At 8 o'clock on the morning of operation, $\frac{1}{6}$ of the total daily dose (0.4 Gm. per kilogram) was administered. All the animals were operated on between 9 a. m. and 12 noon. The time at which the operation was completed was recorded. The drug was administered every four hours as described. Blood was withdrawn at the stated intervals for determination of the level of sodium sulfadiazine in the blood. When death occurred,

TABLE 3.—*Data on Duration of Life and Cultures of Rabbits Used in Crucial Experiment*

A. Series 1.				
Rabbit	Duration of Life, Hr.	Blood Culture	Culture of Wound in Right Lumbar Region	Culture of Wound in Left Lumbar Region
57	Survived	No growth	No exudate	No exudate
58	26	Beta hemolytic streptococcus	Beta hemolytic streptococcus	Beta hemolytic streptococcus
59	24	Beta hemolytic streptococcus, gram-negative bacilli	Beta hemolytic streptococcus, gram-negative bacilli	Beta hemolytic streptococcus, gram-negative bacilli
66	18	No growth	Beta hemolytic streptococcus	Beta hemolytic streptococcus, gram-negative bacilli
67	120	No growth	Beta hemolytic streptococcus	Beta hemolytic streptococcus
68	14	Beta hemolytic streptococcus	Beta hemolytic streptococcus	Beta hemolytic streptococcus
78	42	Gram-negative bacilli	Beta hemolytic streptococcus	Beta hemolytic streptococcus
79	14	No growth	Beta hemolytic streptococcus	Beta hemolytic streptococcus
85	Survived	No growth	Beta hemolytic streptococcus	Beta hemolytic streptococcus
86	18	Beta hemolytic streptococcus	Beta hemolytic streptococcus	Beta hemolytic streptococcus
89	48	No growth	Beta hemolytic streptococcus	Beta hemolytic streptococcus
90	Survived	No growth	No exudate	No exudate
B. Series 2.				
5	Survived	No growth	Staph. albus	Beta hemolytic streptococcus, Staph. albus, Staph. aureus
11	49	Staph. albus	Beta hemolytic streptococcus	Beta hemolytic streptococcus
23	61	Bacillus subtilis	Beta hemolytic streptococcus	Beta hemolytic streptococcus
31	52	No growth	Beta hemolytic streptococcus	Beta hemolytic streptococcus
32	Survived	No growth	Beta hemolytic streptococcus, Staph. albus	Staph. aureus, Staph. albus, gram-positive bacilli, gram-negative bacilli
36	32	No beta hemolytic streptococcus, Staph. aureus	Beta hemolytic streptococcus, gram-negative bacilli	Beta hemolytic streptococcus
43	66	No beta hemolytic streptococcus, B. subtilis	Beta hemolytic streptococcus	Beta hemolytic streptococcus
45	74	No beta hemolytic streptococcus, Staph. aureus	Beta hemolytic streptococcus	Beta hemolytic streptococcus
47	37	No beta hemolytic streptococcus, B. subtilis	Beta hemolytic streptococcus	Beta hemolytic streptococcus
64	24	Beta hemolytic streptococcus, Staph. albus, Staph. aureus	Beta hemolytic streptococcus	Beta hemolytic streptococcus
74	18	No beta hemolytic streptococcus, diphtheroid bacilli	Beta hemolytic streptococcus	Beta hemolytic streptococcus
92	22	No beta hemolytic streptococcus, Staph. albus	Beta hemolytic streptococcus	Beta hemolytic streptococcus

the time of death was noted. The 19 animals which died were submitted to autopsy, the thoracic cavity was opened, and heart blood removed for culture. The wounds were inspected and opened, and cultures were taken under aseptic precautions. There was no actual cellulitis or evidence of spreading infection in any case. When the skin sutures were removed, it was found that in a few instances the crushed muscle segment had become extruded from beneath the fascia. The muscle segment in most of the wounds showed beginning gross

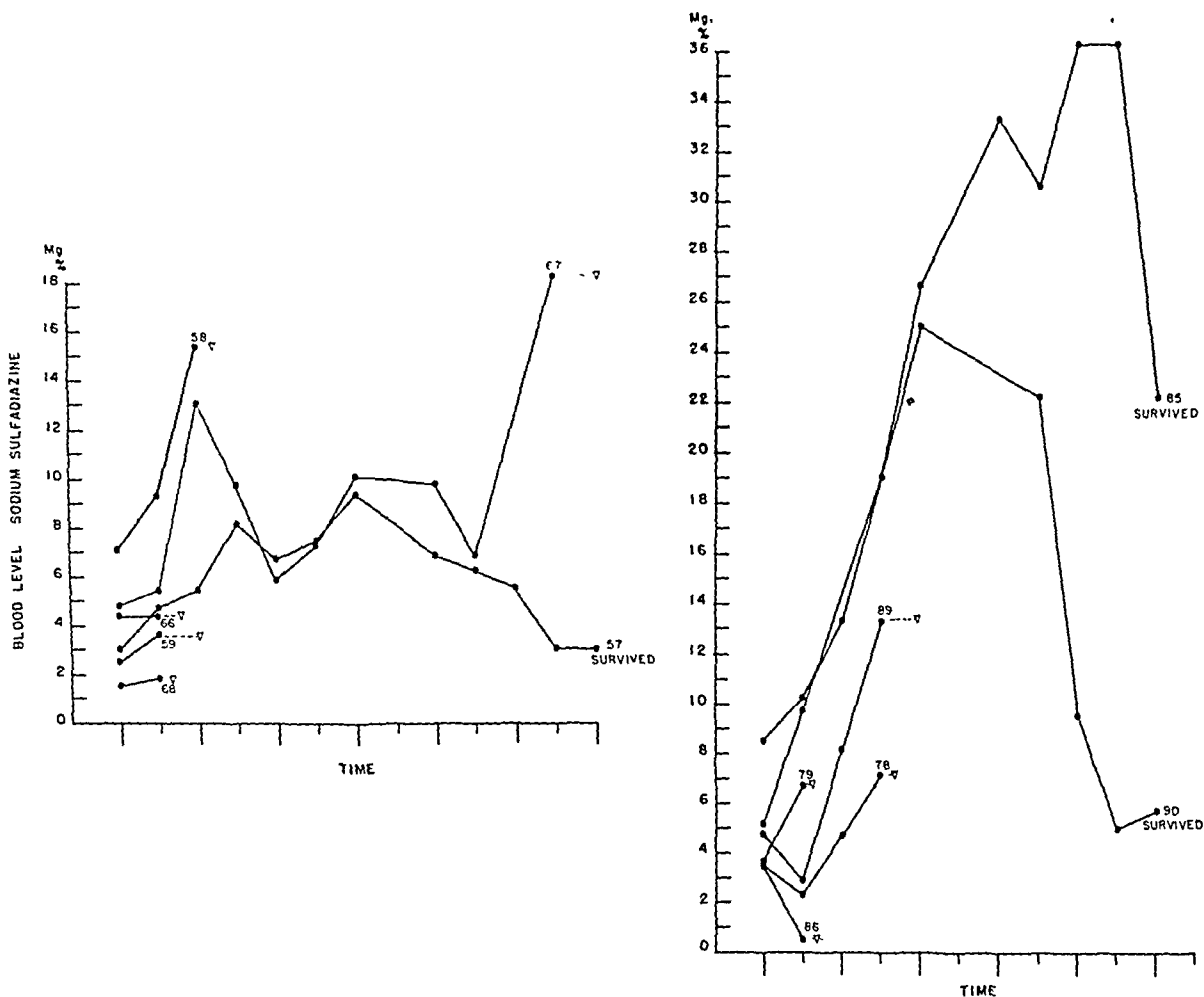


Chart 2.—Blood levels of sodium sulfadiazine for rabbits used in crucial experiment, series 1. In this and the following chart the levels are charted in groups of 6 for convenience in reading. Time is indicated in twelve hour intervals; the broken lines with triangles signify that the rabbit died.

autolysis. In all cases the depth of the cavity on the right was found to be practically dry when the cotton was removed, while in all instances the wound on the left contained a minute amount of an odorless exudate. The appearance

of the wounds in the treated animals was not grossly different from that of the wounds in the inoculated control rabbits.

The animals which survived four days were examined as follows: Blood was removed from the aural vein for culture. The dressing of gauze impregnated with collodion was removed from the wounds; the latter were inspected, and an effort was made to evacuate exudate. If this was possible, cultures were made. Thus, the blood from all rabbits was cultured; the material for culture was taken from the ear of 5 rabbits which survived and from the heart of 19 rabbits which died. Cultures were made from the wounds of 3 of the 5 surviving rabbits. From the other 2, no exudate could be obtained. The results of the making of

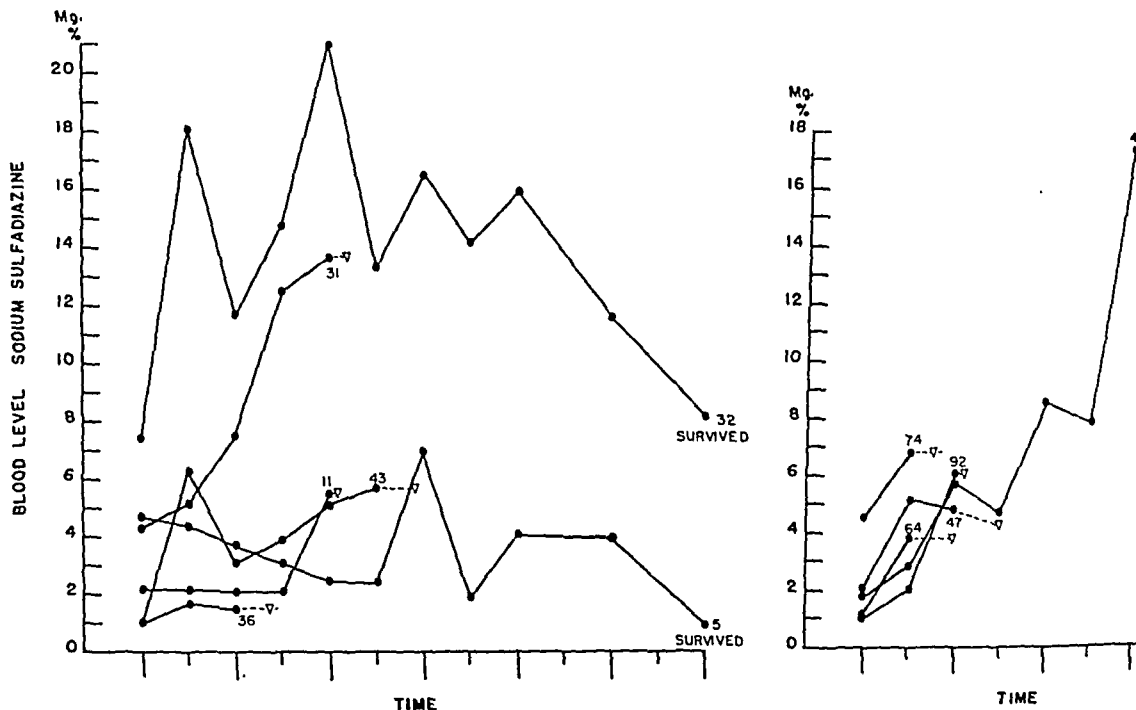


Chart 3.—Blood levels of sodium sulfadiazine for rabbits used in crucial experiment, series 2.

these cultures of the wounds and of blood from the heart or the ear and the length of time of survival are shown in table 3. The data on the inoculated control rabbits are given in table 2.

Charts 2 and 3 show graphically the blood level of sodium sulfadiazine in milligrams per hundred cubic centimeters and the survival period in the crucial experiment.

Summary (see table 4).—Control Group 2 (Inoculation): In examining the cultures of the 12 control rabbits inoculated with a culture of beta hemolytic streptococcus of known virulence, it was found that all blood cultures were positive except 1 and that all wound cultures were positive. The average survival period of 11 of these animals that died was thirty-two hours; 1 animal lived.

Crucial Experiment (series 1): In the first crucial experiment only 4 blood cultures were positive for beta hemolytic streptococcus, while 8 failed to yield a growth of these organisms. All wounds but four (2 rabbits) had an exudate in them which was positive for beta hemolytic streptococcus. The average survival period of 9 of these animals that died was thirty-six hours; 3 animals survived.

Crucial Experiment (series 2): In the second series of the crucial experiment only 1 blood culture was positive for beta hemolytic streptococcus, while 11 failed to show growth. All animals but 1 had wound exudate with beta hemolytic streptococcus. The average survival period of 10 of these animals that died was forty-three and four-tenths hours; 2 animals survived. In all animals except 1 there was an exudate in the wounds from which the beta hemolytic streptococcus was grown.

TABLE 4.—*Data on Death, Positive Blood Cultures and Survival Time of Rabbits in Control Group 2 and Those Used in the Crucial Experiment*

	Rabbits	Died	Positive Blood Cultures	Average Survival Time, Hr.
Control group 2.....	12	11	11	32
Crucial experiment, series 1....	12	9	4	36
Crucial experiment, series 2....	12	10	1	43.4

COMMENT

In these experiments a lethal amount of culture of beta hemolytic streptococcus of known virulence was placed in the wounds of rabbits. The average survival period of 12 control animals was thirty-two hours; all but 1 had positive blood cultures. When sodium sulfadiazine (0.4 Gm. per kilogram of body weight) was given to similar animals at four hour intervals, the survival period of the animals that died was slightly increased; 5 animals (20.8 per cent) lived, and the blood became sterile, although there was no consistent blood level concentration of the drug. The bactericidal action of the drug is evident as far as the blood stream is concerned. The failure of the drug to affect the growth of the organisms in the wounds was not unexpected, and it is probable that the absorption of toxin from the wounds was the cause of death, even though the blood was rendered sterile.

The drug is quickly taken up by the blood stream when given subcutaneously, and it is likewise so rapidly lost from the blood stream that frequent administrations are necessary if the blood stream is to contain a sufficient amount of the drug to be bactericidal. The apparent lack of effect on the bacteria in the wound following the administration of the drug by this method suggests the advisability of placing the drug directly in the wound.

CONCLUSIONS

Sodium sulfadiazine (0.4 Gm. per kilogram of body weight) given subcutaneously to rabbits every four hours did not result in a constant blood level concentration of the drug.

This amount of the drug given in this manner was bactericidal for beta hemolytic streptococcus in the blood.

Sodium sulfadiazine prolonged the survival period of rabbits having wounds inoculated with a known culture of beta hemolytic streptococcus; 5, or 20.8 per cent, of the animals survived in a series of 24.

Sodium sulfadiazine (0.4 Gm. per kilogram of body weight) given subcutaneously did not result in sterilization of the wounds containing devitalized muscle or devitalized muscle plus a foreign body (cotton).

SULFADIAZINE IN EXPERIMENTAL STREPTOCOCCIC INFECTION

A STUDY OF THE EFFECTS OF LOCAL IMPLANTATION

BARTON McSWAIN, M.D.

AND

FRANK GLENN, M.D.

NEW YORK

In another paper¹ we report the results obtained by the subcutaneous administration of sulfadiazine sodium (the monohydrate sodium salt of 2-sulfanilamidopyrimidine) to rabbits with wounds inoculated with a measured amount of culture of beta *Streptococcus haemolyticus* of known virulence. This study represents the results of the implantation of sulfadiazine (2-sulfanilamidopyrimidine) into similar wounds at the time of operation.

METHOD

The method was the same as that previously described. Rabbits weighing 2,200 to 3,800 Gm. were used. With the animal under anesthesia induced by intravenous administration of pentobarbital sodium supplemented by light open drop ether inhalation and by means of aseptic technic, a longitudinal incision of 2 cm. was made posteriorly 1 cm. to the left of the midline and 2 cm. caudad to the lowest rib. The incision was carried down to the sacrospinalis muscle, and with a brass cork borer 1 cm. in diameter, a segment of this muscle 2 cm. in depth was removed. An eighteen hour old broth culture of the NY 5 strain of the beta hemolytic streptococcus, a culture containing 100,000,000 organisms per cubic centimeter, was used; 0.1 cc. of this culture was placed in the wound. The muscle segment was crushed with an artery clamp and replaced, and the wound was closed with silk. An identical procedure was carried out on the right side except that a pledget of dry cotton 1 cm. square and 2 mm. in thickness was placed in the wound before the muscle was reinserted. A gauze dressing impregnated with collodion (4 per cent solution of pyroxylin in a mixture of ethyl oxide and alcohol) was applied. In the control animals only the procedure just outlined was done.

In a group of 6 animals, five minutes, and in a group of 12 animals, sixty minutes, were permitted to elapse after establishing the wounds, and then 0.2 Gm. of sulfadiazine was implanted in each wound. Sulfadiazine instead of its sodium salt was used because of the higher pH of the latter. The drug was sterilized by heating to 120 C. in a dry oven for twenty-five minutes. The amount of sulfadiazine

From the Department of Surgery of the New York Hospital and Cornell University Medical College.

1. McSwain, B., and Glenn, F.: Sodium Sulfadiazine in Experimental Streptococcus Infection, Arch. Surg., this issue, p. 223.

implanted was obviously an excess as far as ideal conditions for wound healing are concerned; only a small part of the powder was dissolved immediately.

Blood was obtained from the ear veins at hourly intervals for six hours and then twenty-four, thirty-six and forty-eight hours after operation. At no time was there more than a faint trace of sulfadiazine detectable in the blood.

In cases in which death occurred, the time was noted, and postmortem inspection of the wounds and cultures of the heart blood and the wounds were made. In cases in which the animal survived, blood for culture was removed from a vein in the ear one week after operation, the cutaneous sutures were removed, the wounds were inspected, the skin edges were pulled apart, and material was removed for culture.

RESULTS

The wounds of the control animals showed no actual cellulitis; however, they showed local necrosis of the muscle and the fascia for an area

Results of Implantation of Sulfadiazine into Wounds Inoculated with a Culture of a Strain of the Beta Hemolytic Streptococcus

Group	Rab- bits	Positive Cultures									
		Died		Survival Time		Blood		Wounds			
		No.	Per Cent	Total, Hr.	Average, Hr.	No.	Per Cent	Right		Left	
Control	9	9	100	842	93.5	9	100	9	100	9	100
Treated	18										
Five minute interval	6	4	66.6	564	141	3	50	5	83.4	5	83.4
Sixty minute interval	12	10	83.4	1,516	151.6	6	50	11	91.7	12	100

of approximately 1 cm. around the incision, gross autolysis of the muscle segment, a small amount of thin odorless exudate and only loose agglutination of the edges of the skin incision.

No difference could be detected between the appearance of the wounds of the animals treated with sulfadiazine five minutes and those treated sixty minutes after inoculation with the streptococcic culture. However, the wounds of the treated animals differed from those of the controls in that in the former there was less local necrosis, less autolysis of the crushed muscle segment and better healing of the skin and the fascia. The amount of undissolved sulfadiazine present varied from approximately one-half the original amount twenty-four hours after operation to complete absorption one week later.

The mortality rate was lower in the experimental than in the control animals (table). Likewise, the average survival time was longer in the treated animals than in the controls. The fact that the average survival time for the animals treated sixty minutes after inoculation with the

culture was longer (one hundred and fifty-one and six-tenths hours) than that of animals treated five minutes after inoculation (one hundred and forty-one hours) can be explained only on the basis of experimental error. The organism was recovered from the blood of only half the treated animals but from the blood of all the controls. There was a slightly lower percentage of positive wound cultures for the treated animals.

SUMMARY AND CONCLUSIONS

Sulfadiazine implanted into wounds experimentally inoculated with a culture of a strain of the beta hemolytic streptococcus resulted in: (1) decreased mortality rate; (2) increased survival time; (3) lower percentage of positive blood cultures; (4) slightly lower percentage of positive wound cultures; (5) apparent improvement in wound healing.

Although there is experimental evidence that the local implantation of sulfanilamide and its derivatives interferes with the healing of clean wounds,² this study indicates that it favors the healing of contaminated wounds.

The favorable effects enumerated were evidently due to the local action of the drug since no more than a faint trace was detectable in the blood.

In one series five minutes was permitted to elapse and in another series sixty minutes between the inoculation of the animal with the streptococcic culture and the implantation of the drug. In these two series no difference was noted in the results obtained; this indicates the full effect of the local implantation of sulfadiazine as long as one hour after the time of contamination.

The action of sulfadiazine was not prevented by the presence in the wound of traumatized muscle.

2. Allen, H. S., and Mason, M. L.: The Effect of Sulfanilamide on the Rate of Healing of Tendons, to be published.

VALUE OF CHEMOTHERAPY IN THE TREATMENT OF OSTEOMYELITIS

ABRAHAM O. WILENSKY, M.D.

NEW YORK

This communication concerning the clinical effect of sulfanilamide and its derivatives as chemotherapeutic aids in the treatment of the various forms of osteomyelitis contains: (1) a résumé of the technical information necessary for the use of these drugs; (2) a résumé of clinical factual experience; (3) a discussion of these facts based on the causative mechanism, the development and the pathology of osteomyelitis and the biologic mechanism according to which these drugs produce their effects; (4) a summary of the conclusions to which these résumés necessarily lead regarding the efficacy of present day chemotherapy.

TECHNICAL INFORMATION NEEDED IN THE ADMINISTRATION OF SULFANILAMIDE AND ITS DERIVATIVES

General Administration.—(a) Administration by Mouth: Administration of sulfanilamide and its derivatives by mouth is the method most commonly employed, and its general principles are so well known that there is no need of repetition. Suffice it to emphasize that in the beginning the drug is pushed so that a concentration of 10 to 15 mg. per hundred cubic centimeters of blood is obtained as rapidly as possible. The method generally used is that of Long and Bliss.¹ Most of the drugs are rapidly absorbed from the gastrointestinal tract in about four hours and rapidly excreted so that the drug should be given frequently and in adequate doses.

(b) Administration by Rectum: Evidence shows that sulfanilamide is absorbed from the rectum and the colon whether administered in the form of solutions or suppositories.² Solutions give a higher concentration in the blood. There seem to be no marked differences in results when the drug is given by rectum rather than by mouth and nausea is

1. Long, P. H., and Bliss, E. A.: Para-Aminobenzenesulfonamide and Its Derivatives: Clinical Observations on Their Use in the Treatment of Infections Due to Beta Hemolytic Streptococci, Arch. Surg. **34**:351 (Feb.) 1937.

2. Turell, R.; Marino, A. W. M., and Nerb, L.: Studies on the Absorption of Sulfanilamide from the Large Intestine: Results Following the Administration of Suppositories, Ann. Surg. **112**:417 (Sept.) 1940.

practically eliminated by this method. When nausea from administration by mouth is present, the rectal route can be substituted.

(c) Subcutaneous Administration: Azosulfamide³ is the preparation most often used for subcutaneous injection. Absorption is somewhat more rapid, but otherwise there seems to be no difference from the results obtained with the oral method.

Solutions of sulfanilamide can be used for continuous subcutaneous injection. Most investigators⁴ have used an 0.8 per cent solution in physiologic solution of sodium chloride. The Council on Pharmacy and Chemistry of the American Medical Association⁵ advised a 1 per cent solution made up in physiologic solution of sodium chloride or, better still, in one-sixth molar racemic sodium lactate solution. The same total dosage is employed for parenteral as for oral administration. Either injections at intervals of four to six hours or a continuous injection should be given. Continuous injection is advisable for patients showing severe toxic manifestations. In 1 case in my personal experience use of the method was not continued long enough to be conclusive.

(d) Intravenous Administration: Sulfapyridine sodium (the monohydrate salt of 2-[paraaminobenzenesulfonamido]-pyridine) seems to be the drug most suited for intravenous administration. A suitable concentration is most rapidly reached and maintained, and since the method is indicated for patients with especially severe toxic manifestations, large doses are advised. In 18 cases in which intravenous administration was carried out by Whittemore, Royster and Riedel,⁶ there was no local or systemic reaction. Nausea occurred in only 1 case; the therapeutic effect was rapid, but there was difficulty in maintaining blood levels constant. I have used this method myself in 1 case of severe cranial osteomyelitis following disease of the frontal sinuses with intracranial complications; the results were negative.

Both the subcutaneous and the intravenous method of administration can be used in the immediate postoperative period and until the drugs can be administered by mouth in order to thwart infection in cases in

3. Azosulfamide is disodium-4-sulfamidophenyl- α -azo-7'-acetyl-amino-1'-hydroxy-naphthalene-3', 6'-disulfonate. This substance has been known as prontosil soluble, as prontosil and as neoprontosil.

4. Lockwood, J. S.: Sulfanilamide in Surgical Infections: Its Possibilities and Limitations, J. A. M. A. **115**:1190 (Oct. 5) 1940.

5. Sulfanilamide, report of the Council on Pharmacy and Chemistry, J. A. M. A. **114**:326 (Jan. 27) 1940.

6. Whittemore, W. L.; Royster, C. L., and Riedel, P. A.: Intravenous and Rectal Administration of Sulfapyridine in Pneumococcic Pneumonia, J. A. M. A. **114**:940 (March 16) 1940.

which contamination during operation is likely or in cases of grossly contaminated traumatic wounds involving bone.

(e) Administration of Sulfanilamide Dissolved in Plasma: Bécart and Philippe⁷ correlated their data with those of previous investigators and noted the value of human blood plasma solutions of sulfanilamide in comparison with total blood and artificial solutions in emergency situations such as are present with military wounds. They stressed the bactericidal and bacteriostatic power of the sulfanilamide-medicated plasma. The mixture can be administered either intramuscularly or intravenously. Since no grouping is required, the method is free from agglutination accidents. The mixture is not affected by conditions of temperature and can easily be transported where it is needed. Its usefulness seems to be enhanced by the observation that plasma does not deteriorate as rapidly as stored blood. The whole subject, however, requires fuller investigation.

Local Use of Chemotherapy.—There are a number of reports in the literature on the effect of the instillation or the application of sulfanilamide and its derivatives in infected bone wounds or fractures either for prophylactic or for therapeutic purposes or for both. I have been able to collect the following:

Key and Burford⁸ found that the implantation of crystals of sulfanilamide in experimental contaminated compound fractures in dogs lessened the danger of subsequent development of infection and did not retard healing. It did not, however, permit closing of grossly contaminated wounds. The usual débridement is necessary, as well as a single layer of suture to retain the serum, which becomes saturated with the drug. Immobilization is important. This is much more important, perhaps, in the treatment of military wounds. The method can be useful also in operative bone wounds in which infection might take place.

Furstenberg⁹ used sulfanilamide locally in several defects of the skull after operation for osteomyelitis and also in the mastoid cavity. He

. . . is confident that sulfanilamide has a desirable local influence which hastens repair, lessens the purulent discharge and brings about a more rapid recovery from wound infections. These factors obviously favor the healing of wounds, . . . [and he has] observed a number of mastoids close promptly and com-

7. Bécart, A., and Philippe, B.: Le plasma humain sulfamidé; ses avantages dans la transfusion d'urgence en absence d'un donneur de sang frais, *Presse méd.* **48**:535 (May 22-25) 1940.

8. Key, J. A., and Burford, T. H.: Local Implantation of Sulfanilamide in Compound Fractures, *South. M. J.* **33**:449 (May) 1940.

9. Furstenberg, A. C.: Personal communication to the author.

pletely within eleven to fifteen days. Of course, these experiments are in their infancy. . . .

The experience of the Mayo Clinic was given by Mayo and Miller¹⁰ and by Herrell and Brown.¹¹ Either the crystals or a thick suspension of sulfanilamide was used. Experimental and clinical observations tended to indicate that the local administration of sulfanilamide and its derivatives exerts a definite beneficial effect in the course of infected wounds in a certain number of cases. This is true of postoperatively infected wounds as well as of wounds which may result either from accidental injuries or from injuries incidental to war. They expressed the opinion that the local use of sulfanilamide and its derivatives is of greater value in the prevention of infection than in the treatment of already well established infection. The results are by no means uniform, but they are encouraging enough to justify continuation of the use of the procedure. Among the various cases in which the method was tried there were 2 cases of chronic osteomyelitis.

Spink and Paine¹² reported the following experience:

. . . A number of patients having chronic osteomyelitis had been previously treated with sulfathiazole [2-(paraaminobenzenesulfonamido)-thiazole], administered orally. No apparent beneficial effect was observed. Two patients were treated by placing five grams of sulfathiazole crystals into the infected area. The first patient, a seven-year old female, had osteomyelitis of the tibia. A sinus leading to the bone and the involved portion of the bone were debrided, sulfathiazole was placed in the bony defect. A plaster cast was placed on the extremity. Four days later, the wound was examined through a window cut in the cast. It appeared clean, but staphylococci were isolated from the wound. Additional crystals were placed in the cavity, and the patient was sent home. Three months later examination revealed the wound to have healed, and an x-ray film showed extensive replacement of the defect in the tibia by new bone. A second patient has been treated recently in a similar manner, and further time must elapse before an opinion can be expressed concerning the effect of this therapy.

Combined General and Local Use of Chemotherapy.—At the University of Hamburg, in Germany, a combination of the general and the local use of chemotherapy was tried out by Gottesbüren.¹³ Prontosil (compound not stated) was given for its general effect. In complications involving joints it was instilled directly into the joints. Gauze treated

10. Mayo, C. W., and Miller, J. M.: Solution of Sulfanilamide in the Local Treatment of Wounds, Proc. Staff Meet., Mayo Clin. **15**:609 (Sept. 25) 1940.

11. Herrell, W. E., and Brown, A. E.: Solution of Sulfanilamide in the Local Treatment of Wounds, Proc. Staff Meet., Mayo Clin. **15**:609 (Sept. 25) 1940.

12. Spink, W.: Personal communication to the author. Spink, W., and Paine, J. R.: Sulfathiazole in Staphylococcal Infections, Minnesota Med. **23**:615 (Sept.) 1940.

13. Gottesbüren, H.: Die Behandlung der akuten und chronischen Osteomyelitis in der Chirurgischen Universitätsklinik Hamburg-Eppendorf, München. med. Wchnschr. **86**:1378, 1939.

with 10 per cent dimethyldisulfanilamide (N^1, N^1 -dimethyl- N^4 -sulfanilyl-sulfanilamide) was used in the wounds. However, no decisive effect was noted.

Adjuvant Action of Other Drugs and Forms of Therapy.—(a) Neoarsphenamine: The combination of sulfanilamide with neoarsphenamine has been advised. I have had no experience with this combination, but it seems that such experience as there has been should be further corroborated.

(b) Heparin: Possibly because of the work which was done in the treatment of bacterial endocarditis with heparin,¹⁴ Lyons¹⁵ has used heparin as an adjuvant when the ordinary surgical methods and chemotherapy did not produce results. I understand that Lyons has had some good results with the combination of heparin and chemotherapy.

(c) Gas Gangrene Antiserum: During the past several years I have used the combination of a prophylactic dose of gas gangrene antiserum with sulfanilamide prior to operations in which there was a possibility of postoperative development of infection by *Clostridium welchii* with or without other types of infection. No such infection developed in any of the patients. In traumatic bone wounds (civil or military) this combination might be valuable as a prophylactic.

(d) Radiotherapy: Radiotherapy and chemotherapy (sulfanilamide) were used by Woodward¹⁶ in combination. This combination of methods has no clinical contradiction, but owing to the small number of cases in which it was employed, the results are inconclusive.

Relative Value of Drugs and Dosages.—There is no absolute agreement as to which of the drugs is best except that sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) seems to work best with pneumococcic infections. My own experience is that, all things considered, sulfanilamide worked best in the general run of cases of surgical infection; and in cases of the latter type of infection none of the derivatives has seemed superior. Apparently it is the custom to change from one to the other drug if no satisfactory results are quickly obtained; but in 2 of my own cases of severe infection in which this change was made, no perceptible difference was noted. Some of the observers have put great reliance on sulfathiazole. Sulfamethylthiazole (2-[paraaminobenzenesulfonamido]-4-methylthiazole) produces too many toxic mani-

14. Kelson, W.: A New Method of Treatment of Subacute Bacterial Endocarditis, Using Sulfapyridine and Heparin in Combination: Preliminary Report, J. A. M. A. **113**:1700-1702 (Nov. 4) 1939.

15. Lyons, C.: Personal communication to the author.

16. Woodward, F. D.: Osteomyelitis of the Skull: Report of Cases Resulting from Frontal Sinus Infections with Staphylococcus, J. A. M. A. **95**:927 (Sept. 27) 1930.

festations; but in a case of mine in which this drug was tried after the others, no superior effect was noted. The use of azosulfamide was advised by Horan and French¹⁷ when maximal concentration is desired in minimal time. The intravenous injection of sulfapyridine sodium is advised for a similar reason; but in 1 of my cases in which this was employed, no effect was noted.

There must be some difference between pneumococcic pneumonia and the general run of surgical infections. In my experience with the latter group of infections, the results have not been anywhere near so striking as the results obtained by physicians in treating pneumonia.

There is no complete agreement as to the best method of administering these drugs. The main index of the sufficiency of the chemotherapeutic agent is the concentration in the blood,¹⁸ and in order to know for certain what this is, blood determinations are necessary. Since the therapeutic aim is to attain a concentration in the blood of 10 to 15 mg. per hundred cubic centimeters as rapidly as possible, all available routes of administration should be used—oral, subcutaneous, intravenous and intramuscular. Intrathecal administration is superfluous because it was noted by Marshall¹⁹ and others that the concentration in the cerebrospinal fluid is close to the concentration in the blood. Not all patients of the same weight respond similarly to identical dosage, and one should therefore vary the dosage with different patients according to the concentration attained in the blood. It is usually advisable to continue therapy for a few days after clinical recovery in order to prevent relapse. Infants tolerate the drugs well; the dose for them is from one third to one half of the adult dose. Children require from one half to three fourths of the adult dose.

EFFECT OF CHEMOTHERAPY ON CERTAIN PHYSIOLOGIC PROCESSES

Effect on Cross Matching Tests.—Because various reports had drifted in that there was difficulty in making cross matching tests after the institution of chemotherapy, an investigation of this problem was made by Kreinin²⁰ and associates, which confirmed the fact that such difficulty occasionally exists. It was their opinion, however,

17. Horan, V. G., and French, S. G.: Prevention of Mastoiditis: Survey of Six Hundred and Twenty-One Cases of Acute Otitis Media Treated with Sulfanilamide, *Lancet* **1**:680 (April 13) 1940.

18. Bratton, A. C., and Marshall, E. K., Jr.: New Coupling Component for Sulfanilamide Determination, *J. Biol. Chem.* **128**:537 (May) 1939.

19. Marshall, E. K., Jr.: The Determination of Sulfanilamide in the Blood and Urine, *Proc. Soc. Exper. Biol. & Med.* **36**:4221 (April) 1937.

20. Kreinin, S.: The Effect of Sulfanilamide in the Cross Matching of Blood, *J. Lab. & Clin. Med.* **25**:690-692 (April) 1940.

. . . that the inability to cross match blood following the administration of sulfanilamide is due to changes in the blood brought about by the disease requiring the use of sulfanilamide rather than to the drug itself.

Effect on Bacteriophage Action.—There have been many reports on the effect of antiseptics on bacteriophage. According to Jern and Meleney,²¹ bacteriophage is susceptible to, and is destroyed by, certain of the stronger antiseptics. There is a differential susceptibility to some of the weaker antiseptics; the phages of *Staphylococcus* are regularly more susceptible than those of *Bacillus coli*. The latter in turn are more susceptible than those of *Bacillus pyocyaneus*. Therefore, antiseptics in general cannot be used with bacteriophages in the treatment of mixed infections. Zinc peroxide is no exception to this rule.

Sulfanilamide, sulfapyridine and azosulfamide do not interfere with bacteriophage action. It is therefore possible to combine the use of sulfanilamide and sulfapyridine with that of bacteriophage in treating those mixed infections which are caused by hemolytic streptococci combined with staphylococci or the colon bacilli. This combined method has been used with gratifying results in a number of cases.

Influence on Anesthesia.—I am indebted to Dr. G. H. van Gilluwe²² of the anesthesia staffs of the Flower and Fifth Avenue Hospitals and the St. Vincent's Hospital for the thought that owing to the diminution of the oxygen content of the body (cyanosis-anoxemia) as a toxic manifestation of the use of these drugs and because of the crippling of the oxygen-carrying function of the blood by the formation of methemoglobin and sulfinmethemoglobin, as well as the frequent reduction in the red cell count, it is wise to be more generous with the use of oxygen during the maintenance of inhalation anesthesia in any patients treated with sulfanilamide and its derivatives. He has seen several deaths associated with this situation.

CLINICAL EXPERIENCE WITH CHEMOTHERAPY IN THE TREATMENT OF OSTEOMYELITIS

Acute Primary Osteomyelitis (Direct Infection in Accidental and Operative Bone Wounds).—On following the lead given by the use of sulfanilamide and its derivatives in infected wounds, the prophylactic use of these drugs seems especially indicated in all accidental bone wounds and in all operative bone wounds in which infection might be expected to take place. This should not relieve one of the responsibility of employing all the usual and well tried procedures (i. e., cleansing and débridement for accidental bone wounds and aseptic technic for operative

21. Jern, H. Z., and Meleney, F. L.: Effect on Bacteriophage of Prontylin, Prontosil, Sulfapyridine and Other Antiseptics and Dyes Used in Surgical Practice, *J. Lab. & Clin. Med.* **24**:1017 (July) 1939.

22. van Gilluwe, G. H.: Personal communication to the author.

wounds) which have endured through many years of successful practice. According to Jensen, Johnsrud and Nelson,²³ the chemotherapeutic drug for prophylactic use should be in crystalline form; Spink and Paine¹² stated that it should be used in an oily suspension or base; Mayo and Miller¹⁰ and Herrell and Brown¹¹ recommended its use as a thick suspension in a saline solution. The outer wound should be arranged so that the drug will be retained and not eliminated in the discharge from the wound. In spite of the fact that previously ordinary methods have attained success in a high percentage of cases, the helpful action of sulfanilamide and its derivatives should be added prophylactically in suitable cases in view of the good reports in the literature as a consequence of the use of these drugs in infected wounds.

Should the wound communicate with a joint, the chemotherapeutic drug can be instilled directly into the joint.

In certain types of operation (especially those used on the intestines and particularly in posterior operations for carcinoma of the rectum) in which the necessity for resection of the coccyx and the sacrum exists, I have used sulfanilamide prophylactically for several days before the operation for the purpose of lessening or eliminating postoperative osteomyelitis in the stump of the resected bone. It is my distinct impression that the number of such infections has been materially lessened thereby. In addition, I have used sulfanilamide powder locally in the operative fields in which infection is present or likely to occur at the conclusion of the procedure with most satisfactory results.^{23a}

Acute Hematogenic Osteomyelitis, with Special Reference to the Long Bones.—The literature does not contain as large a number of reports concerning the use of chemotherapy in cases of hematogenic osteomyelitis of the long bones as it does of the use in cases of extension osteomyelitis of the skull following acute infection of the nose and nasal accessory sinuses or following acute infection of the middle ear with extension to the mastoid process and temporal bone. I herewith give résumés of the more pertinent accounts in the literature which I have been able to find.

In a 10 day old male infant, whose history is reported by Carroll and associates,²⁴ staphylococcic septicemia developed from an infected umbilicus. No effect was produced by the administration of azosulfamide

23. Jensen, N. K.; Johnsrud, L. W., and Nelson, M. C.: Local Implantation of Sulfanilamide in Compound Fractures, *Surgery* 6:1 (July) 1939.

23a. Wilensky, A. O.: The Local Prophylactic Use of Chemotherapy (Sulfanilamide) After Intra-Abdominal Operations Against the Development of Postoperative Infection, *M. Rec.* 155:61 (Jan. 21) 1942.

24. Carroll, G.; Kappel, L.; Jones, L.; Gallagher, F. W., and Dirocco, F. W.: Sulfamethylthiazol: A Report of Its Clinical Use in Staphylococcus Septicemia with Apparent Success; Report of Animal Experiments, *South. M. J.* 33:83 (Jan.) 1940.

or sulfapyridine. The septic process involved the left knee joint, the right shoulder joint and the right hip joint in succession. Sulfamethylthiazole was then given, and the septic symptoms subsided within twenty-four hours. The infant recovered, but when last seen he had necrosis of the head of the right humerus.

Thornhill, Swart and Reel's ²⁵ case was one of osteomyelitis of the femur with a high grade of toxicity and a growth of *Staphylococcus aureus* in the blood cultures (5 colonies per cubic centimeter). Sulfanilamide was given from the beginning with a blood concentration of 3.5 mg. The general sepsis as shown by the blood cultures improved slowly, and the blood became sterile only after one month. No real or apparent effect was noted except that seen ordinarily without the use of chemotherapy.

Melton ²⁶ reported 5 cases of osteomyelitis in which the patients were treated with sulfathiazole. In the first case, one of acute osteomyelitis of the radius and the ulna after open reduction of a fracture, there was improvement but no clearing-up after treatment with sulfapyridine. Sulfathiazole was then given to a total of 26 Gm. After each injection the patient complained of headache and vomited, but marked improvement took place. In a case of acute osteomyelitis of the lower end of the humerus, pyrexia persisted after the administration of sulfathiazole but subsided after the drainage of a subperiosteal abscess. In the third case, one of acute osteomyelitis of the upper end of the femur, clearing-up was effected by sulfathiazole. In the fourth case, in which the lower end of the femur was affected, there was pyrexia after drainage; this subsided after treatment with sulfathiazole. In the fifth case there was acute osteomyelitis of the ilium and suppurative arthritis of the hip; the blood culture yielded a growth of *Staph. aureus*. No improvement was noted after the administration of sulfathiazole, and the blood culture still showed *Staph. aureus*.

I am inclined to say that chemotherapy had no effect in some of these cases because of the presence of associated lesions (e. g. abscesses, arthritis) which required operation.

Schein's ²⁷ case was one of infection of the spine by *B. pyocyaneus*. Sulfanilamide was given to the patient for nine days for a total of 27 Gm. A temperature of 106 F. dropped to normal in two days. Administration of the drug was later discontinued because of anorexia, depression and disorientation. One and one-half weeks later there was recurrence of fever; the temperature was up to 102 to 103 F. Sulf-

25. Thornhill, W. A.; Swart, H. A., and Reel, C.: Sulfanilamide in *Staphylococcus Septicemia*, J. A. M. A. **113**:1638 (Oct. 28) 1939.

26. Melton, G.: Sulfathiazole in *Staphylococcal Infections*, J. A. M. A. **115**:471 (Aug. 10) 1940.

27. Schein, A. J.: *Pyocyaneus Osteomyelitis of the Spine: Report of Case of Successful Treatment with Sulfanilamide*, Arch. Surg. **41**:740 (Sept.) 1940.

anilamide was again given for a total of 34 Gm. The temperature again subsided. A diagnosis of vertebral osteomyelitis was confirmed roentgenographically several weeks later, and healing took place after the patient was put in a spinal brace. The final opinion was that sulfanilamide controlled the original sepsis but did not prevent the localization in the spine.

It is difficult to evaluate this case because toxic symptoms compelled the interruption of chemotherapy and then fever recurred, which in turn subsided after further chemotherapy. There is the possibility that the secondary rise of temperature had a purely local cause and that its subsidence had no relation to the chemotherapy.

Mitchell²⁸ treated 5 patients for severe acute osteomyelitis with dimethyldisulfanilamide in addition to the ordinary forms of treatment. All did well; the condition of 2 of them had seemed hopeless because of the signs of general sepsis, and the impression is conveyed by the report that the good effect had special reference to this aspect alone.

This experience undoubtedly indicates the good effect of chemotherapy on the general infection *per se*; this good effect is especially well exemplified in the cases of the 2 patients whose condition seemed hopeless.

Spink¹² treated 5 patients for acute osteomyelitis and septicemia with sulfathiazole. In each instance coincidentally with the administration of the drug the blood cultures became sterile. There was little or no effect on the bone lesion itself. Spink formed the impression that in cases in which the condition is acute chemotherapy (in this case the use of sulfathiazole) may localize the lesion in the bone, thus limiting the extent of the lesion. He stated that according to his still limited experience chemotherapy does not otherwise affect the local lesion once it is present. On the other hand, his experience supports that of others that chemotherapy is and will continue to be of great use in the control of general infection.

In Carey's²⁹ experience the response to chemotherapy (sulfanilamide) of osteomyelitis caused by the beta hemolytic streptococcus was unpredictable; but chemotherapy (sulfanilamide) should always be instituted because in cases of acute septicemia the infection may be more rapidly localized, the fever reduced and the blood sterilized. Occasionally the chronic form of the disease may be cured by chemotherapy. In cases of staphylococcic osteomyelitis neither sulfanilamide nor sulfapyridine seemed to have much effect, but sulfathiazole seemed to have some definite antistaphylococcic effect.

28. Mitchell, A.: Treatment of Acute Osteomyelitis by Uleron, Brit. M. J. 2:1200 (Dec. 10) 1938.

29. Carey, B. W.: Use of Sulfanilamide and Related Compounds in Diseases of Infancy and Childhood, J. A. M. A. 115:925 (Sept. 11) 1940.

Goldberg and Sachs³⁰ reported 2 cases in which chemotherapy was used. Sulfanilamide did not have any effect as shown in the blood cultures, which continued positive, but after five days' use of sulfapyridine the blood became sterile. The local lesion was treated by drill holes and the general condition with transfusions. The local signs of inflammation disappeared within three days. Nevertheless, there were roentgen evidences of well marked bone lesions. Goldberg and Sachs commented on the fact that such beneficent sterilization of the blood is seen daily in the absence of chemotherapy.

Chemotherapy has been discarded by Dunkmann,^{30a} and he has relied entirely on ordinary surgical procedures in the treatment of osteomyelitis. Apparently chemotherapy has given him no superior results.

The case of Rosenthal and Vogel³¹ was one of Staph. aureus osteomyelitis of the humerus treated continuously with 95 Gm. of sulfapyridine. This case is mentioned only to show the harmful effect of the drug; lymphocytic granulocytopenia developed, and the patient, a child, died one month later.

In treating staphylococcic osteomyelitis in general, particularly in the bacteremic phase, Lyons¹⁵ has employed the following measures: (1) surgical management of the suppurative focus, incision and drainage of the focus, excision of the focus or ligation of the major vein draining that focus; (2) administration of sulfathiazole in doses sufficient to maintain a blood concentration of 5 mg. per hundred cubic centimeters; (3) the clinical use of heparin when infections have not been controlled by the procedures already mentioned; he has expressed the opinion that the latter procedure has a definite place in the treatment of osteomyelitis.

My own experience, while limited, has in each instance been informative; I shall give the report of the most illustrative case.

An inflammatory focus developed in the upper end of the tibia of a young boy. Sulfanilamide, sulfapyridine and sulfamethylthiazole were all administered, but the blood culture continued to show a few colonies of staphylococci in spite of the fact that the clinical manifestations seemed better. Then a thrombosed saphenous vein was palpated, and when all of the thrombosed portion was excised, its origin could be traced directly into the involved head of the tibia. Excision of the vein was immediately followed by sterilization of the blood.

In this case there was roentgen evidence of osteomyelitis, and the opinion was expressed by others that the atypical (?) and benevolent course was due to the chemotherapy. I disagree as to this (1) because

30. Goldberg, S. L., and Sachs, A.: Sulfapyridine in Treatment of Staphylococcus Aureus Bacteremia, J. A. M. A. **113**:1639 (Oct. 28) 1939.

30a. Dunkmann, G.: Die Osteomyelitis und ihre Prognose, Ergebn. d. Chir. u. Orthop. **32**:527, 1939.

31. Rosenthal, N., and Vogel, P.: Granulocytopenia Caused by Sulfapyridine in Children, J. A. M. A. **113**:584 (Aug. 12) 1939.

I have had many experiences in which a similar course (with the exception of thrombosis of the saphenous vein) was noted without chemotherapy and (2) because excision of the vein seemed to be the turning point toward recovery. I am inclined to say that chemotherapy had a doubtful value in this case. In any event, since the drug was adequately administered from the beginning of the illness, I feel certain that it had no preventive value with regard to the bone lesion and certainly no value at all in sterilizing the blood.

Primary Osteomyelitis of the Skull.—Primary osteomyelitis of the cranial bones, being a direct infection in a traumatic or an operative wound, is the sort of disease which should receive prophylactic treatment with sulfanilamide and its derivatives both generally and locally. Undoubtedly this use will receive its fullest application in the treatment of military wounds, and this subject is most apropos now. However, no experience is available at present which could guide one except that resulting from chemotherapy applied generally and locally to infected wounds.

Hematogenic Osteomyelitis of the Skull.—An original site for hematogenic infection of the skull is extremely rare, and in most of the relatively few cases that have been recorded the lesions were metastatic either secondary to an original lesion in one of the long bones or simultaneous therewith. I have been unable to find any experience with this condition recorded in the literature, and I have none of my own. Offhand, I should say that whatever experience with hematogenic osteomyelitis in the long bones is available is applicable to hematogenic osteomyelitis of the skull.

Extension Osteomyelitis of the Skull.—Extension osteomyelitis of the skull is intimately bound up with primary nasal accessory sinusitis and with otogenic infection, and all discussion must necessarily take into account the effects of chemotherapy on the preceding infection: (1) the prophylactic effect in the prevention of extension to the cranial bones; (2) the therapeutic effect in the treatment of osteomyelitis itself; (3) the prophylactic effect in the prevention of the intracranial complications which so frequently occur, and (4) the therapeutic effect in the treatment of the latter.

(a) *After Disease of the Accessory Nasal Sinuses:* In the early stages of infection and in cases of mild infection strictly limited in scope to the nasal accessory sinuses, chemotherapy seems to be unnecessary, since in most of these cases spontaneous resolution and cure occur. In cases of severe infection of the nasal accessory sinuses with high fever, chemotherapy seems to act favorably in bringing down the fever according to Kramer³² and Kulkin.³³ However, Kramer remarked that the

32. Kramer, R.: Personal communication to the author.

33. Kulkin, S.: Personal communication to the author.

"discomfort associated with the administration" of the drug "outweighs in most cases the benefits attained by the reduction in temperature." The indiscriminate use of sulfanilamide and its derivatives should be deprecated, and certainly use by the general public without adequate medical supervision should be restricted. In any event, the course of the infection should be carefully watched and controlled because of the tendency of these drugs to mask the development of any spread into the cranial bones. Further, because of this, it seems to be the consensus that chemotherapy cannot be used in a prophylactic way against the development of any bone complication (e. g., osteomyelitis).

During the early stages of the development of osteomyelitis of the cranial bones, chemotherapy seems to have a somewhat favorable effect on the general clinical manifestations (e. g., fever), even while the bone lesion is advancing. Aside from this, however, the following varied experience is available: The effectiveness of Furstenberg's⁹ use of chemotherapy was doubtful because it was necessary to combine surgical intervention with it immediately. At the University of Illinois Fabricant's³⁴ experience was frankly disappointing; at the Mayo Clinic, according to Adson,³⁵ chemotherapy was "effective in the early stages of the disease [osteomyelitis] but of little or no value once sequestration had taken place." In Kramer's³² experience, chemotherapy was fruitless in the treatment of established osteomyelitis. Mosher³⁶ expressed the opinion that chemotherapy is dangerous because of an undue reliance which may be put on the drug to the exclusion of the necessary surgical procedures. In all reported cases the administration of these drugs has tended to obscure the further development of the clinical and the pathologic picture and the development of dangerous complications.

My own experience parallels that of others in every way: Chemotherapy has not prevented the occurrence of osteomyelitis of the cranial bones. Chemotherapy has tended to mask the development and the spread of infection into the cranial bones. Once osteomyelitis was established, chemotherapy has had no effect, and surgical eradication of the disease has been necessary.

I have had one personal experience with extension osteomyelitis of the skull. The notes are as follows:

When a young girl 15 years of age returned from a camp at the end of summer, a head cold developed, followed by pain in the right frontal sinus and orbital cellulitis. Intranasal manipulation directed into the nasofrontal duct having proved ineffective, open operation on the frontal sinus was performed by the attending rhinologist, and complete eradication of the frontal sinus with drainage of the orbital abscess was done. At the same time the right antrum and the

34. Fabricant, N. D.: Personal communication to the author.

35. Adson, A. W.: Personal communication to the author.

36. Mosher, H. P.: Personal communication to the author.

ethmoid sinuses were cleared out. Temporary improvement followed, but about two weeks later typical signs of osteomyelitis of the right half of the frontal bone (pain, tenderness, swelling and edema) appeared, and a roentgenogram showed well marked disease of the bone.

The patient was then transferred to my care. I excised the whole of the right half of the frontal bone and revised the site of the previous operation on the frontal sinus. Again there was improvement for about ten days, followed by spread of the disease to the left half of the frontal bone. I operated for the second time and removed about two thirds of the left frontal bone and did a radical operation on the left frontal sinus.

Several days later generalized headache developed, sometimes referable to both mastoid regions; the ears, however, were normal. Gradually thereafter the condition became worse. Neurologic evidences of meningeal irritation followed, and a spinal tap showed fluid containing approximately 150 cells with gram-positive cocci. However, the cocci were never identified, and the cellular content of the spinal fluid at first increased and toward the end diminished. Finally, the patient passed into stupor and coma and eventually, approximately two months after the beginning of the illness, died from an intracranial complication which, because of the atypical generalized signs and the laboratory findings, I thought was encephalitis.

During the entire illness and from its inception the patient was given adequate doses of sulfanilamide and later of sulfathiazole and still later subcutaneous injections of sulfanilamide and finally intravenous injections of sodium sulfapyridine. At no time during the entire illness did the chemotherapy seem to have a clinical effect of any kind; the pathologic condition and the intracranial complication developed and seemed to progress uninfluenced by any of the drugs employed.

(b) After Infection of the Middle Ear and the Mastoid Process of the Temporal Bone: Osteomyelitis of the mastoid and petrous portions of the skull occurs as a spread by contiguity from an infection of the lining membrane of the aural and associated cells of the mastoid process. In turn, disease of the mastoid process can spread by contiguity of structure into the squamous or zygomatic processes of the temporal bone and cause osteomyelitis of the temporal bone proper.

Pediatricians report favorable prophylactic results from chemotherapy in the early stages of otitis media; in these stages, however, favorable results are common without chemotherapy. Great caution and careful observation are necessary in these early stages for fear the drug may mask the developing clinical picture.

Bowers'³⁷ results indicate that when sulfanilamide is regularly given early before bone softening has occurred, operative work is decreased by half. Late treatment doubled the operative indications as compared with those in patients treated early and adequately. In the experience of Horan and French¹⁷ the incidence of mastoiditis after the introduction of sulfanilamide therapy was only 3.4 per cent, compared with the previous 22.7 per cent. They expressed the opinion that the use of

37. Bowers, W. C.: Observations of Seven Hundred and Ninety-Three Cases of Acute Purulent Otitis Media, with Chemotherapy in Three Hundred and Ninety-Six Cases, *J. A. M. A.* **115**:178 (July 20) 1940.

sulfanilamide and its derivatives will greatly reduce the incidence of mastoiditis and will allow a more conservative attitude to be adopted if mastoiditis develops. Bowers' experience paralleled this: "Chemotherapy has unquestionably added greatly to the confidence of physicians in their ability to conquer acute otitis media and mastoiditis."

Hebble³⁸ accepted as well established the fact that the earlier the drug is employed in treatment the better the results. Hebble's custom has been to operate on all patients in whom otorrhea continues beyond the sixth week, regardless of any temporarily favorable effects which chemotherapy may show, in order to avoid intracranial involvement and late chronic deafness.

Bowers stated that in general there was poor response to chemotherapy before operation, even when sulfanilamide was employed for longer periods and in larger doses in the absence of toxic symptoms. A somewhat similar response may be expected after operation, but the drug has the tendency to mask certain typical symptoms.

Clinical experience with sulfanilamide at the Massachusetts Eye and Ear Infirmary led Converse³⁹ to the opinion that sulfanilamide should be reserved for the treatment of spreading or life-endangering infections and that it should not be used as an adjunct to the usual measures for the treatment of infections of minor severity. He gave three reasons for this belief:

1. Premature initiation of drug therapy has made complete clinical evaluation of the patient difficult and has obscured progress of the infection to complicating endophlebitis.

2. There have been recurrence and further spread of the infection after omission of sulfanilamide in patients who clinically appeared to be healed, so that it is clear that the use of sulfanilamide necessitates fairly extensive laboratory studies to confirm the clinical impression of subsidence of the infection.

3. The amount of sulfanilamide required to sterilize a focus of infection is so large that the danger of toxic manifestations necessitates hospitalization of all patients receiving the drug.

Converse stated that the demonstrated evidence creates an obligation because of the aforementioned reasons to continue sulfanilamide therapy, if once begun, until there is bacteriologic as well as clinical evidence of complete subsidence of the infection. Premature cessation of chemo-

38. Hebble, H. M.: Sulfanilamide in Treatment of Acute Infections of the Ear and Mastoid in Infants and in Children: Quantitative Study of Seventeen Cases, *Arch. Otolaryng.* **31**:808 (May) 1940.

39. Converse, J. M.: Recurrence of Otitic Infections Due to the Beta-Hemolytic Streptococcus, Following Inadequate Sulfanilamide Therapy, *J. A. M. A.* **113**:1383 (Oct. 7) 1939.

therapy on clinical evidence alone permits exacerbation and recrudescence of infection in a patient with an ill prepared defensive mechanism.

Latency of symptoms is commented on by all observers.⁴⁰ Because the apparently too early interruption of chemotherapy has been followed by unheralded intracranial complications after a period in which there was apparently more or less complete cessation of symptoms, Bowers has continued chemotherapy for a week after the subsidence of all symptoms and has had no complications since this method was inaugurated.

Chemotherapy has caused streptococcus mastoiditis to be just as misleading as mastoiditis due to Pneumococcus type III. The picture becomes deceptive; signs of meningitis may become apparent even when the local signs have decreased and mastoid involvement is not suspected, and the potential consequences become more dangerous and difficult to determine.

Chemotherapy in the Treatment of Intracranial Complications of Extension Osteomyelitis of the Skull.—There are more hopeful reports in the literature regarding the use of chemotherapy in the treatment of intracranial complications of osteomyelitis of the skull. According to Kramer,³² in rhinologic cases,

. . . the complications due to lymphatic and vascular involvement, with and without meningitis, have responded amazingly to sulfanilamide and its derivatives. For the first time in rhinologic practice, recoveries have been obtained in patients with these complications. [It has been] found . . . absolutely necessary, however, to attack surgically the source of the infection to obtain permanent cure.

At the Mayo Clinic, Adson³⁵ also has found chemotherapy to be

. . . of value in controlling and curing a number of patients with meningitis. It is of questionable value once a brain abscess has developed, but judging from . . . experience . . . it is quite effective if given in the early stages of acute encephalitis.

In the cases in which the complications have followed otologic infection, chemotherapy has had a greater trial. Maybaum^{40a} and associates use chemotherapy (sulfanilamide) alone in the treatment of otitic complications, viz., meningitis, sinus thrombosis and abscess of the brain. Removal of the bone focus or other localized lesion (extradural abscess) is imperative, but in the presence of extreme bacterial meningitis intensive chemotherapy is advised for twenty-four to thirty-six

40. (a) Maybaum, J. L.; Snyder, E. R., and Coleman, L.: Experiences with Sulfanilamide Therapy for Otogenous Infections, with Special Reference to Masking of the Clinical Course, *Arch. Otolaryng.* **30**:557-575 (Oct.) 1939. (b) Smith, H. B., and Coon, E. H.: Meningitis Due to a Hemolytic Streptococcus: Report of Two Cases with Recovery After Use of Prontosil and Sulfanilamide, *ibid.* **26**: 56 (July) 1937.

hours prior to operation. In the presence of complications, sulfanilamide is given, and any local focus is eradicated. In cases of petrositis chemotherapy is dangerous during the period of observation because of the tendency to mask the clinical picture, but once the diagnosis is made, sulfanilamide should be given in addition to any operative manipulation. This drug is especially useful in cases of continued otitic sepsis, even though localized foci have been surgically eradicated.

Experienced aural surgeons have always been most apprehensive of intracranial complications. Chemotherapy has introduced a peculiar antagonistic effect. On the one hand, chemotherapy may so mask the symptoms that apparently symptomless meningitis may develop; on the other hand, chemotherapy is establishing a dominating place for itself in the successful treatment of meningitis. In the twenty-five years prior to 1936, only 76 recoveries from streptococcic meningitis were reported in the literature; since 1936, over 200 recoveries have been reported. Mortality has dropped from 97 to 35 per cent. This is a great comfort and a signal achievement. Success in treating intracranial complications, according to Maybaum and associates,^{40a} follows only when the original focus has been thoroughly eradicated, because while sulfanilamide is effective in clearing body fluids of streptococci, it is not effective when the bacteria are locked up in osseous tissue.

In the only personal experience I have had with intracranial spread of infection (described previously), chemotherapy seemed to have no effect. Sulfanilamide, azosulfamide, sulfathiazole and sodium sulfapyridine were used by mouth, by hypodermic injection, by continuous subcutaneous infusion and by the intravenous route.

Chemotherapy in the Treatment of Dentoalveolar Infections.—Only a few oral surgeons and dentists are ready to make definite statements regarding the use of chemotherapy in the treatment of dentoalveolar infections and their complications. Some, with whom I have discussed the matter, have expressed the opinion that it has been of help.⁴¹ Apparently some dramatic results occur; this is evidenced by a case related to me by Goldberg.^{41a}

A young boy 12 years of age had acute infection of the left second upper bicuspid with swelling of the face, a temperature of 106 F. and cyanosis. After extraction of the root, pus was evacuated, and a diagnosis of maxillary sinusitis with possible extension to the cavernous sinus was made. Chemotherapy was employed in connection with proper surgical drainage, and recovery followed.

I have not been able to find any reported experience with the prophylactic use of chemotherapy in the prevention of osteomyelitis of the jaws following dentoalveolar infection. Stern's experience

41. (a) Goldberg, H.: Personal communication to the author. (b) Winter, L.: Personal communication to the author.

included 4 cases in which osteomyelitis developed despite previous chemotherapy and continued to develop until sequestration occurred.

I am indebted to Dr. L. Stern⁴² for the following experience: Topical application has been valuable in diminishing pain, periostitis and lymphadenitis. It reduces the period of postoperative treatment following minor operations (extractions, root end resections and cyst extirpations) from 85 per cent in a control group to 12 per cent in the group treated with chemotherapy. Sulfanilamide was somewhat more effective than its derivatives. Besides reduction of temperature and restriction of swelling no effect of chemotherapy was noted in cases with associated abscess, and operation was always necessary.

COMMENT

Only those cases of acute osteomyelitis due to the ordinary pyogenic bacteria, staphylococci and streptococci will be discussed. Ordinary acute hematogenic osteomyelitis is commonly due to infection by *Staph. aureus*. Extension osteomyelitis of the skull after infection of the nasal accessory sinuses is more commonly due to streptococci of the hemolytic and nonhemolytic type. Extension osteomyelitis following otologic infection is most commonly due to streptococci and pneumococci. Primary osteomyelitis (infected traumatic wounds of bone) wherever it occurs is due to a variety of organisms depending on environmental and causal conditions. Commonly these organisms belong to the colon groups; and in military wounds they form the commonest cause as a fecal infection due to the unnatural conditions of army life in the field. In considering the effects of treatment with sulfanilamide and its derivatives, the bacterial findings should be kept in mind since the various drugs exhibit different potencies with the various classes of bacteria.

For a proper understanding of chemotherapy it is necessary to review the essential characteristics of bacterial infection both as a general phenomenon involving the body as a whole and as a local phenomenon involving any particular area, tissue or organ of the body—in this instance, bone.

Infection occurs in the animal body in one of the following ways:

1. Local infections. Localized areas of infection occur on the surface of the body (i. e., the skin, the mucosa of the alimentary canal, the lining of the genitourinary tract), and no general effect on the body as a whole is perceptible to the person affected or to the unaided senses of the examiner or is discoverable by any laboratory method. Cultures of the peripheral blood show no growth of any organisms. Equally commonly, only one such episode occurs and is followed by permanent cure; or there is a succession of such episodes separated by intervals of apparently

42. Stern, L.: Personal communication to the author.

complete health. These are minor infections, and the use of chemotherapy in their treatment is not necessary or advisable.

2. Local infection with generalized effect. Localized areas of infection similar to those just described occur, but evidences of varying degrees of intensity are present to show that the body as a whole is affected by the infection. The perceptible evidences include fever with or without chills, subjective symptoms of general intoxication and cultures of the peripheral blood which may or may not show a growth of organisms. Commonly only one such episode occurs—any bacteremia is only temporary—and complete cure follows. Relatively rarely, retrogression of the general infection is interrupted by recrudescence of the infection. Then the infection may progressively increase until the subject is overwhelmed, or secondary retrogression to cure may follow either undisturbed or with further subsequent similar interruption. Chemotherapy may not be necessary or advisable in cases without symptoms of general intoxication and without positive blood cultures. As soon, however, as the latter are present, chemotherapy should be administered intensively because chemotherapy has its greatest effect in the stage of general infection.

3. General infections. Clinical and/or laboratory evidence of general bacterial invasion of the body may occur (1) without any discoverable evidence of the primary local lesion or (2) in the presence of a demonstrable primary local lesion. In this group the general infection dominates the clinical picture either temporarily or permanently and in the majority of the cases is accompanied by bacteremia, demonstrable by culturing the peripheral blood. The number of colonies of growth in the culture plates form a convenient measure of the intensity of the general infection, and a comparison of repeated blood cultures may be used as a measure of the further progression or of any lessening of the infection and of improvement in the clinical picture. Hence the greatest opportunity for chemotherapy exists as the physical and the distribution characteristics of the bacterial invasion most nearly approach test tube conditions and permit intimate contact between bacteria and the chemotherapeutic agent. Clinically, this corresponds to the presence of living bacteria in the blood stream (i. e., bacteremia).

The essential mechanism for such general infection is undoubtedly an infected clot in a vascular channel in which the growth of organisms occurs on that surface of the clot bordering freely circulating blood. The continual shedding of organisms into the circulating blood forms the physical basis for bacteremia (general infection). In actual practice the infected clot may be (1) accessible or (2) inaccessible for surgical ligation or removal.

1. Accessible infected thrombi of this nature as they occur in general surgical practice are part and parcel of thrombophlebitis. Classic

examples of this are jugular thrombosis after mastoid infection of the process of the temporal bone and the occurrence in the case of osteomyelitis reported in this communication.

In actual practice chemotherapy has no sterilizing effect when an infected clot of this sort keeps shedding bacteria into the general circulation. To sterilize the blood, it is necessary to eliminate the offending segment of blood vessel which contains the infected thrombus by excision. The case cited previously presents an almost laboratory proof of this statement.

2. The outstanding grossly observable example of inaccessible infected thrombi is endocarditis with active bacterial growth in the vegetations of the valves. It is true that in cases of general infection without demonstrable local lesions, endocarditis of this kind is frequently present at post-mortem examination. Even though chemotherapy has previously been mostly a failure in cases in which the infected thrombi were inaccessible, even when heparin has been added, a number of brilliant recoveries from cavernous sinus thrombophlebitis have recently been reported.

In laboratory practice this endocarditis corresponds to a surface culture (plate or tube) in which bacterial growth heaps itself up on the surface of the medium and does not extend into the depths. All activity and effect of the bacterial accumulation occurs on the surface and is readily counteracted by any fluid medium which may cover it. Such bacterial growth, in contradistinction to that which may be caused to develop in the depths of a culture medium, is easy of access in the maximum degree to any antibacterial agent which may be brought in contact with it so that growth of the organisms is most easily inhibited or totally stopped with or without death of the organisms themselves.

Bacterial growth in the depth of a culture medium parallels growth in the depth of any thrombus; neither is much or at all affected by the superimposed drug. In the depths, bacterial growth continues, perhaps with much diminished activity. Should the drug be removed too soon, bacterial growth in either case eventually reaches the surface and begins to flourish there again—in the test tube as a renewed surface activity, in the thrombus or in a locked-away focus of infection (as in a bone) as a renewed clinical manifestation with recrudescence of symptoms and unexpected or masked continuation of the pathologic process or, perhaps, by the appearance of important complications. This explains why in certain cases chemotherapy is ineffective in preventing continued pathologic changes, why masking of the symptoms and the lesion occurs and is so frequently commented on and why complications are not prevented and make sudden unheralded appearances.

In progressively increasing bacteremia, the increase in the number of bacteria is due to growth in the original vascular clot, to the increment in other such vascular clots as metastatic foci are formed and, possibly,

rarely to growth of the bacteria in the circulating blood stream. The difficulties of successful chemotherapy under such conditions are proportionately increased.

In any case with clinical or laboratory evidence of general bacterial infection, secondary (metastatic) foci occur in various tissues and organs of the body. When local physical conditions are appropriate, any or all of the secondary foci may act in turn as points of departure for additional infection. In cases of osteomyelitis, secondary or metastatic foci of infection in other bones or in other tissues of the body commonly form important parts of the total clinical picture. As far as can be learned from the literature, chemotherapy does nothing to prevent the appearance or the development of such metastatic foci.

As a physical phenomenon, infection appears as: (1) a localized area on an external surface of the body (the skin, the mucous membrane of the alimentary canal or of the genitourinary tract, the conjunctivas); (2) a localized area on a surface lining one of the body cavities (the pleural or the peritoneal cavity or the meningeal or the pericardial space); (3) a localized area buried in the depths of a solid tissue organ (muscle or bone) or in a fascial space, or (4) a general bacterial infection, evidenced most commonly by a positive blood culture with or without a demonstrable local lesion.

With infection of the first type, usually, though not always, there is little or no clinical evidence of effects of the bacterial activity on the body as a whole. With the second, third and fourth types, it is the rule to have clinical evidence of the effects of the bacterial activity on the body as a whole. Frequently with the second and third, and always with the fourth, type there is, in addition, laboratory evidence (positive blood cultures) of the presence of bacteria in the peripheral circulation. Chemotherapy as related to the physical phenomenon of infection is successful in direct proportion to the possibility of intimate contact between the chemotherapeutic agent and the bacteria.

A localized lesion may show pathologic anatomic or physiologic effects because of: (1) the presence and the activity of active living bacteria (the effect of chemotherapy on a lesion of this type is not always predictable, but there are many reports in the literature of some striking successful effects); (2) the effect of thrombosis and embolism (this is most marked in a bone in which the physical conditions of the circulation are such that thrombosis [blockage] of a major vessel may deprive a segment of the bone of nutrition, and this mechanically causes necrosis of tissue; chemotherapy has no effect on these purely mechanical consequences); (3) any enlargement of a local lesion bordering on a cavity or space (skull to subdural space, bone to joint) resulting in mechanical bursting of an area of liquefaction with consequent spreading of the infection to the entire surface of the adjacent space or cavity (the effect of chemo-

therapy in the treatment of these accidents is unpredictable and difficult of interpretation).

Any general infection (with or without demonstrable bacteremia) produces pathologic anatomic and/or physiologic effects: (1) by virtue of the production of bacterial toxins of sufficient amount and/or intensity to produce pathologic effects varying from a perceptible but unimportant degree to that in which the entire body is overwhelmed and death follows; (2) by virtue of the production of thromboembolic lesions in various organs and tissues with the production of secondary (metastatic) foci; (3) by virtue of the simultaneous occurrence of both of these mechanisms.

In the treatment of general surgical infections, the effects of chemotherapy have up to now been unpredictable. Many times this is due to the difficulty of reaching the provocative local lesion or even of discovering it. In osteomyelitis, the bone lesion is secondary to a general infection, which in turn is due to some preceding primary lesion (e. g., a furuncle). The demonstrable bacteremia may be due to a continuance of activity in the primary lesion or to activity in the local bone lesion. In any event I have come to know that chemotherapy is not successful when a local lesion provocative of bacteremia is still present and that surgical eradication of such a local lesion is necessary if chemotherapy is to be successful.

Chemotherapy in the Treatment of Hematogenic Osteomyelitis.—Acute hematogenic osteomyelitis is a bacterially infected embolus blocking a more or less important vascular channel in a bone with all of its consequences. In the absence of demonstrable bacteremia or general infection, there are certain local consequences. The least important of the consequences is local bacterial infection; this either is controlled by the proper antibacterial forces of the body or results in an abscess (subperiosteal, with or without extension into the soft parts and intramedullary abscess). The local infection becomes important only when it is communicated in some way to a neighboring joint or to a contiguous cavity (pericardial, pleural, meningeal). The most important local consequence of blockage by a thrombus or an embolus is the disturbance or total exclusion of the blood supply from the corresponding segment of bone supplied by the affected vessel, with consequent necrosis and sequestration; all of this is due to a purely mechanical disability usually not much influenced by the infection. The important thing to remember is that the area so blocked off does not come into contact with the freely circulating blood and cannot be reached by any chemotherapeutic agent contained therein.

Chemotherapy in the Treatment of Chronic Osteomyelitis.—Chronic osteomyelitis and the persistence of open wounds leading down to diseased bone are due to several broad causes: (1) the persistence of infection; (2) the retention of sequestrums (foreign body); (3) the presence

of mechanical conditions which do not permit closure of the wound, and (4) the presence of complicating conditions. The second and third causes are of a purely mechanical nature.

1. Infection persists in small infected thrombi in the diseased area, in small collections of pus enclosed in small bone spaces devoid of proper drainage or in small collections of bacteria locked away in the depths of scar tissue. Access of any chemotherapeutic agent in the blood stream to the local lesion is difficult or impossible because the blood or the lymph supply to such areas is absent or severely limited.

2. Mechanical disabilities in the area of any wound or sinus are uninfluenced by any chemotherapeutic agent. These include sequestrums, insufficient drainage openings, such as a cortical perforation or a canal passing through the thickness of a bone, and a bone cavity with its inability to collapse and permit obliteration of the space.

3. Complicating conditions include especially joint involvement, which operates by adding mechanical disabilities in addition to being a source of reinfection. Both local and general methods of administration of the chemotherapeutic agent are indicated here, but their effect is often unpredictable.

The factors which determine the possibility and efficacy of healing of any acute or chronic osteomyelitis include: (1) the possibility of eradication of the foci of infection by mechanical surgical means or by chemotherapy (because of the absolutely or much diminished blood supply access of the chemotherapeutic agent is not possible or not possible in sufficient concentration); (2) the possibility of revascularization of any compromised bone segment (in proportion as this approaches normal, chemotherapy holds out some possibility of aid); (3) the elimination of any mechanical obstruction to healing (this cannot be influenced by chemotherapy since it is a purely physical disability; but the prophylactic use of these drugs could, perhaps, be advantageous when secondary operations are necessary for the correction or elimination of these mechanical disabilities); (4) the prevention or elimination of any complicating factor (in this phase of the subject the local use of chemotherapy is indicated for complicated infections of neighboring hollow spaces, especially for complicating joint infections; the ordinary general use of chemotherapy is indicated also when complicating joint infections are accompanied by high fever and other signs of general toxicity which are commonly present as a reflection or patent or latent infection).

When bacteria are locked up in the depths of a blood clot (as in a thrombus or an embolus or in part of the body, such as a bone) from which freely circulating body fluids have been excluded by the plugging effect of a thrombus or embolus, the effect of the drug becomes minimal or is entirely absent, and chemotherapy is a failure. This explains the failures in clinical practice, the masking of local signs and the progression

of pathologic changes. Then, too, if part of such an infected clot breaks off or becomes dislodged to travel to and become blocked in a distant part of the body, metastatic lesions can occur and develop in spite of the saturation of the body with the chemotherapeutic drug.

Since in any case of bacterial infection, and especially in one of acute hematogenic osteomyelitis, a most classic example of the latter, the entire pathologic process consists of a general effect on the entire body and a strictly local effect at the point of development of the local lesion, and since the bacteriostatic effect of chemotherapy does not take place in a sequestered portion from which the general circulating fluids of the body are excluded, it follows that in any of these cases the local lesion can and frequently does remain and continues as a latent or masked phenomenon, even though the general symptoms (e. g., fever, toxicity) have shown marked improvement. This masking effect has been commented on and emphasized by all observers, especially the clinicians.

Chemotherapy in the Treatment of Acute Hematogenic Osteomyelitis.—Since acute hematogenic osteomyelitis is a local manifestation of a general bacterial infection in which the initial stage is marked by positive blood cultures, the only stage in which any chemotherapeutic bacteriostatic or bactericidal effect is to be expected is that in which bacteremia is present. When this effect is obtained, that part of the clinical picture which is caused by the presence of living bacteria in the blood stream (i. e., chills, at least part of the fever, toxicity) is either lessened or entirely eliminated in direct proportion to the bacteriostatic or bactericidal effect produced. In effect this leads to amelioration of the general clinical symptoms so that the clinician is led to believe that the local lesion also is improving *pari passu* with the general improvement.

The best effect of chemotherapy occurs in cases of general infection in which bacteria are being transported in the blood stream. Nevertheless, should additional numbers of bacteria be continuously shed into the blood stream from an infected blood clot, chemotherapy will have no apparent effect on positive blood cultures. I have had such an experience in practice myself, in which the positive blood culture was eliminated only after the infected thrombosed vein was excised. The valuable practical lesson which all of this teaches is that chemotherapy has no lasting effect, unless all local lesions potentially provocative of bacteremia have been thoroughly removed by surgical means. This should always be kept in mind when chemotherapy is employed in the treatment of osteomyelitis.

This points to a prophylactic use for chemotherapy. Should one have in mind an operation in infected territory from which bacteria may be derived into the circulation, a sufficient concentration of a chemotherapeutic agent might succeed in inhibiting the activity of the bacteria and in rendering their immediate destruction possible. I have used this principle in the preparation of certain classes of patients and have suc-

ceeded in eliminating certain postoperative reactions and infections which have hitherto occurred.

Beneficent retrogressive changes are commonly seen and have been commonly noted in the clinical histories of many patients with acute osteomyelitis who in past years and before the advent of the new chemotherapeutic drugs have come under the care of all surgeons. Sometimes these beneficent improvements in the various aspects of the clinical, anatomic and pathologic pictures attained remarkable extents and were most gratifyingly surprising when just the opposite outcome seemed imminent. Such unaided spontaneous favorable outcomes undoubtedly are occurring today and will continue to happen. In the new experience with chemotherapy such results also appear and it remains to be seen in the accumulated experience whether the actual and percentage relations will be different or approximately the same. In any event, in making any conclusion as to the action of any of the new chemotherapeutic drugs in the treatment of osteomyelitis, the possibilities for spontaneous recovery should be remembered.

SUMMARY AND CONCLUSIONS

Sulfanilamide, sulfapyridine, sulfathiazole and sodium sulfapyridine can be administered by mouth, by hypodermic injection and by continuous subcutaneous and intravenous infusion. They can also be instilled locally into a wound, dissolved in plasma and reinjected into the circulation and injected into the subdural cerebrospinal space and lumbar puncture. They can be combined with other drugs, as arsphenamine or heparin, with gas gangrene antiserum, with radiation therapy and with blood transfusions. Each of the drugs seems to have a special affinity for a different group or strain of bacteria. The drugs are rapidly absorbed and quickly excreted, so that the dose must be fairly large and frequently administered. They do not interfere with certain physiologic functions, such as blood groupings, with normal antibacterial activities and with bacteriophage action. When carefully administered and checked by repeated laboratory examinations, the drugs are safe to administer, and gastrointestinal and/or hematologic complications can be entirely avoided or markedly ameliorated.

All of these drugs act by inhibiting the biologic activities of the bacteria, which assume a dormant state (bacteriostasis). Destruction of the bacteria (bacteriolysis) is then accomplished by the ordinary antibacterial agencies of the body, and the drugs must be administered for a sufficient length of time and in sufficient concentration to enable the latter to work adequately; otherwise, bacterial activity is not inhibited, and/or symptoms recrudescence, and the disease increases. The drugs act only by intimate contact with the offending bacteria; hence, they act best and perhaps exclusively when the bacteria are in the circulating blood or in the fluid

content of normal cavities or spaces (e. g., the subdural space). When the bacteria are locked away out of ready contact with the circulating body fluids (as in a bone or within a thrombus or an embolus), little or no effect is produced; hence, all of such foci of infection must be surgically eradicated if chemotherapy is to have the desired effect. The failure to eradicate them leads to failure of treatment, from the start or after temporary improvement, to masking of symptoms, to unperceived symptomless advance of the pathologic process, to unexpected recrudescence of the symptoms and to unheralded complications.

All of these facts are particularly applicable to acute osteomyelitis, especially the hematogenic variety, in each of its typical skeletal distributions. A consideration of these criteria should guide one in the proper application of chemotherapy as an aid in the treatment of this condition.

In cases of primary osteomyelitis, the local use in the wound at first, and later, if necessary, the general use of chemotherapy are indicated. In the treatment of extension osteomyelitis, particularly that of the cranial bones, chemotherapy has met with obstacles so far as the prevention of the spread of the disease and of the occurrence of intracranial complications is concerned; in the latter, however, chemotherapy has shown some wonderful results; but even here experience has shown the absolute necessity of removing all local areas of infection. In cases of acute hematogenic osteomyelitis, chemotherapy is especially indicated in the stage of general infection; and the danger of a progressive hidden pathologic process must be kept in mind.

The results of chemotherapy are not always predictable, owing to the various obstacles enumerated in this communication to the efficient exercise of the bacteriostatic power of the drug, to the occasional difficulty of maintaining the proper concentration of the drug, to the necessity of matching the proper drug to the provocative organism, to the occurrence of certain toxic effects of the drugs themselves and to the difficulty inherent in removing inaccessible foci of infection by surgical means, which is always necessary.

In actual practice, the treatment of osteomyelitis with sulfanilamide and its derivatives has not produced the startling results which it has had in the treatment of some medical conditions, notably the various types of pneumonia. The observed results have varied all the way from the absolutely negative to occasional satisfactory effects; but always the results have been unpredictable; these drugs as a rule have not prevented the spread of the disease or the occurrence of complications and in general surgical practice and especially in the treatment of osteomyelitis, have not been as satisfactory as one could wish. Sometimes the proper interpretation of good results is difficult owing to the possibility that such beneficent results have occurred spontaneously, as they have done many times in the past before this form of chemotherapy was available.

EFFECT OF THE ADMINISTRATION OF LIPOCAIC AND CHOLESTEROL IN RABBITS

CORNELIUS VERMEULEN, M.D.

LESTER R. DRAGSTEDT, M.D.

DWIGHT E. CLARK, M.D.

ORMAND C. JULIAN, M.D.

AND

J. GARROTT ALLEN, M.D.

CHICAGO

If rabbits are fed cholesterol in excessive amounts, a marked and sustained elevation of the blood cholesterol level occurs, and after a few months progressive intimal changes appear in the aorta.¹ Cholesterol and other lipids² are deposited in the inner layers of the aorta, and gradually lesions develop which assume most of the characteristics of human arteriosclerosis.³ These findings suggest that this disease may be the result of some metabolic defect and not a necessary accompaniment of the aging process. The abnormally high incidence of presenile arteriosclerosis in patients with diabetes mellitus supports this view. Here also there is evidence that some disturbance in fat metabolism resulting in sustained hypercholesteremia is involved. Rabinowitch,⁴ Joslin⁵ and others have demonstrated that high fat diets given to patients with diabetes favor, and that, conversely, low fat-high carbohydrate diets retard, the appearance of hypercholesteremia and arteriosclerosis. The discovery in this laboratory⁶ of arteriosclerosis in depancreatized dogs

From the Department of Surgery, the University of Chicago.

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with greater incidence than normal for this species presents one more point of resemblance between pancreatic diabetes and diabetes mellitus. The diabetic animals in which this complication developed were maintained on high fat diets with insulin but with inadequate amounts of lipocaic. The role of lipocaic as a second internal secretion of the pancreas has been discussed elsewhere⁷ and will not be reviewed here. Continuous administration of lipocaic along with insulin is necessary for the preservation of pancreatectomized animals; and high fat diets increase, and low fat diets diminish, the need for this substance.⁸

The well known facts that some patients with diabetes are not returned to a normal state by the adequate administration of insulin and that the remaining defects are largely attributable to failure of the normal utilization of fat suggested that in these cases a deficiency in lipocaic production might be present and thus play a role in the development of vascular disease.⁹ It was to test this possibility that the present experiments were undertaken. A preliminary report was published in 1940.¹⁰ During the course of the work a report appeared by Huber, Broun and Casey¹¹ in which it was concluded that lipocaic was effective in preventing cholesterol arteriosclerosis and hypercholesteremia in rabbits. The experiments of Steiner¹² and of Baumann and Rusch¹³ concerning the effect of choline on cholesterol arteriosclerosis are interesting, since choline has an effect on some phases of lipid metabolism similar to that of lipocaic. Steiner concluded that choline given with cholesterol appeared to delay but not to prevent the appearance of arteriosclerosis in rabbits and that the administration of choline alone produced a resolution of aortic lesions previously induced by cholesterol feeding. Baumann and Rusch, on the other hand, were unable to find any preventive effect of choline on the formation of aortic atheroma and hypercholesteremia or on the deposition of fat and cholesterol in the liver produced by the oral administration of cholesterol.

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EXPERIMENTAL PROCEDURE

A total of 77 young rabbits of both sexes were used for this study. They were kept in metabolism cages and fed a commercial rabbit food¹⁴ which was stated to be a mixture made from alfalfa, oats, barley, corn, soybean, wheat, milk, sodium chloride, calcium carbonate and calcium sulfate and to contain protein (15 per cent), fat (3.25 per cent), carbohydrate (62 per cent) and fiber (12 per cent). Varying amounts of cholesterol (0.25 to 1.0 Gm. per day) and several different preparations of lipocaic¹⁵ were employed. The cholesterol was dissolved in sunflower seed oil according to Leary's method,³ and a carefully weighed amount was rolled up into a small ball and placed in the back of the rabbit's mouth. Care was taken to make sure that each dose was swallowed.

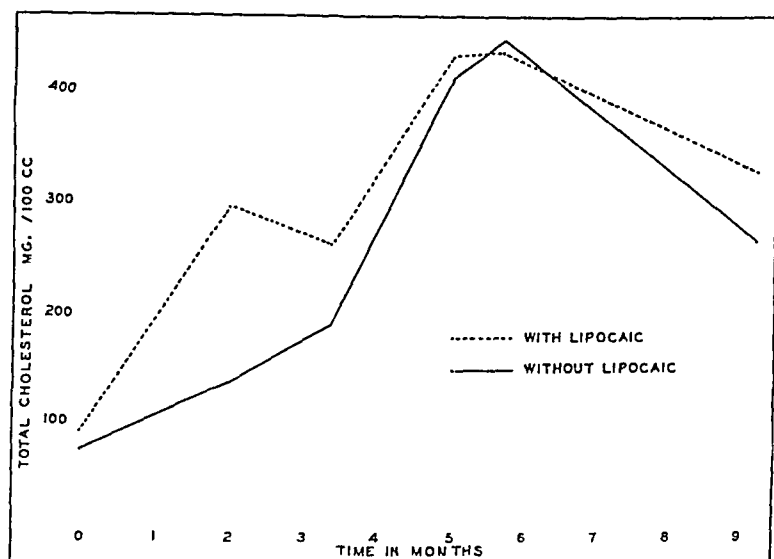


Fig. 1.—Blood cholesterol of rabbits fed cholesterol.

The lipocaic was dissolved in water and placed in the back of the rabbit's mouth with a pipet. Twenty animals received cholesterol alone; 52, cholesterol plus lipocaic, and 5, lipocaic alone. After sixty to three hundred and sixty days of this treatment, the animals were killed and examined. The aorta, the liver, the adrenal glands and the kidneys were studied grossly and microscopically. Blood cholesterol and total lipid determinations were made at intervals throughout the experiment. The livers were analyzed chemically for the cholesterol and the total lipid content. The total lipids were determined by a modification of Bloor's method and the cholesterol by the method of Schonheimer and Sperry.¹⁶

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RESULTS

The curves in figure 1 illustrate the effect of the oral administration of cholesterol and of cholesterol and lipocaic on the blood cholesterol of rabbits. These curves were constructed from averages of all deter-

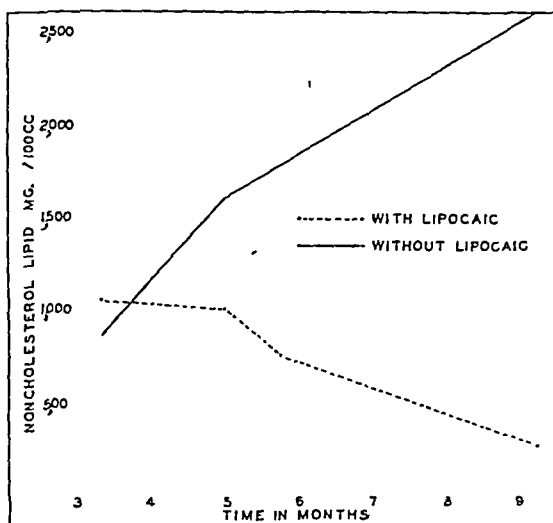


Fig. 2.—Blood noncholesterol lipids of rabbits fed cholesterol.



Fig. 3.—Photograph showing almost identical degree of arteriosclerosis in 2 rabbits receiving cholesterol daily for nine months; 1 of these (rabbit 566) was given lipocaic daily in addition. The adrenal glands of rabbit 566 were somewhat less enlarged than those of the control (rabbit 604).



Fig. 4.—Photomicrograph showing deposition of lipoid material in the greatly thickened intima of the aorta. This rabbit was given 0.25 Gm. of cholesterol daily for five months.

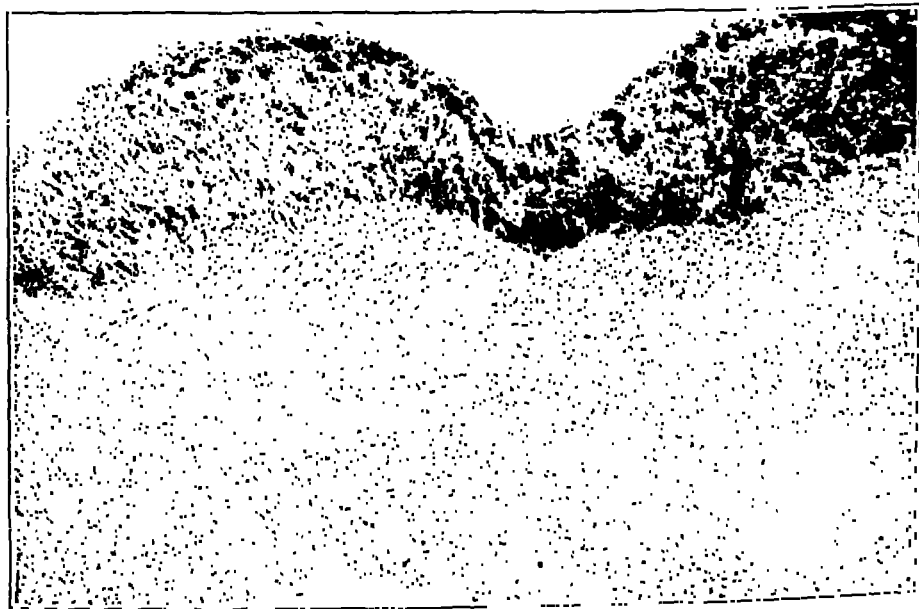


Fig. 5.—Photomicrograph showing similar degree of lipoid deposit in the aorta of a rabbit treated like the rabbit in figure 4 but given lipocaine daily besides.

TABLE 1.—*Effect of Lipocaine on Aortic Lesions Due to Cholesterol*

A. Rabbits Receiving Cholesterol Alone *											
Series 1 (1 Gm. of Cholesterol Daily)			Series 2 (0.25 Gm. of Cholesterol Daily)			Series 3 (0.5 Gm. of Cholesterol Daily)			Series 4 (0.5 Gm. of Cholesterol Daily)		
Duration, Days	Rab- bits	Extent of Lesion	Duration, Days	Rab- bits	Extent of Lesion	Duration, Days	Rab- bits	Extent of Lesion	Duration, Days	Rab- bits	Extent of Lesion
60	3	Severe	150	1	None	120	1	Moderate	60	1	None
			150	2	Slight	180	1	None	180	1	Moderate
			150	1	Moderate	180	1	Slight	300	1	Slight
			150	2	Severe	310	1	Moderate	330	1	None
						310	1	Severe	330	2	Severe
						240	1	Slight			
						270	2	Slight			
B. Rabbits Receiving Cholesterol Plus Lipocaine											
(1 Gm. of Cholesterol Daily; % Daily Dog Dose † of Lipocaine)			(0.25 Gm. of Cholesterol Daily; % Daily Dog Dose † of Lipocaine)			(0.5 Gm. of Cholesterol Daily; ½ Daily Dog Dose † of Lipocaine)			(0.5 Gm. of Cholesterol Daily; ½ Daily Dog Dose † of Lipocaine)		
Duration, Days	Rab- bits	Extent of Lesion	Duration, Days	Rab- bits	Extent of Lesion	Duration, Days	Rab- bits	Extent of Lesion	Duration, Days	Rab- bits	Extent of Lesion
60	2	Slight	150	2	Slight	120	1	Slight	60	2	None
60	5	Moderate	150	4	Moderate	180	1	Slight	180	1	Moderate
60	2	Severe	150	15	Severe	180	2	Moderate	300	1	None
						210	1	Slight	300	1	Severe
						210	1	Moderate	330	1	Slight
						240	2	Moderate	330	1	Moderate
						270	2	Moderate	330	4	Severe
						360	1	Severe			

* Five rabbits were given lipocaine alone, but arteriosclerosis did not develop in any of them.

† A daily dose of 100 gm. of cholesterol and 10 gm. of lipocaine per 1000 gm. of body weight.

* Five rabbits were given lipocaine alone, but arteriosclerosis did not develop in any of them.

† A daily dog dose of lipocaine is defined as that amount which will prevent the development of lipocaine deficiency in the pancreatectomized dog. In the first two series of rabbits a crude extract was used, and each rabbit received an extract of 40 Gm. of raw pancreas. In the third series a preparation made by Eli Lilly & Company was used. In the fourth series a purified extract was given, and each rabbit received 50 mg. of dried material.

minations in each of the two series. They show that a marked rise in the blood cholesterol occurs, which tends to diminish somewhat after five or six months. This confirms the observations of Weinhouse and Hirsch.² The administration of lipocaic in amounts up to half of that required by the depancreatized dog seemed to accelerate this rise and in general to cause hypercholesteremia to persist somewhat longer than it did in the controls. No preventive effect was discerned, contrary to the findings of Huber, Broun and Casey.¹¹

The curves in figure 2 summarize the findings with respect to the effect on the noncholesterol lipids of the blood, chiefly phospholipid and neutral fat. From the hundredth day of the experiment on there occurred

TABLE 2.—*Severity of Aortic Lesions in Rabbits With and Without Lipocaic*

Extent of Lesion	Rabbits Given Cholesterol Alone	Per Cent	Rabbits Given Cholesterol and Lipocaic	Per Cent
None.....	4	20	3	6
Slight.....	5	25	8	15
Moderate.....	4	20	18	35
Severe.....	7	35	23	44
Total.....	20	100	52	100

TABLE 3.—*Chemical Analysis of Livers of Rabbits in Series 4*

	Livers of Rabbits Given Cholesterol	Livers of Rabbits Given Lipocaic and Cholesterol	Livers of Rabbits Given Lipocaic
Average liver weight.....	120 Gm.	130 Gm.	95 Gm.
Average total cholesterol.....	1.13%	0.65%	0.29%
Average total lipid.....	7.4 %	5.16%	4.5 %

a progressive rise in this fraction in the animals receiving cholesterol alone. Weinhouse and Hirsch² also observed this coincident increase in noncholesterol lipids, the phospholipid being increased seven, the neutral fat five, and the total lipid eleven times above the normal value. The addition of lipocaic to cholesterol produced a striking change, of which the explanation is at present obscure. While the blood cholesterol rose rapidly in these animals, the noncholesterol lipid fell. At nine months, the average noncholesterol lipid value in the first group was 2,600 mg. per hundred cubic centimeters; in the group receiving lipocaic it had fallen 250 mg. per hundred cubic centimeters.

The data on the incidence of arteriosclerosis and the effect of prophylactic lipocaic therapy are given in table 1 and summarized in table 2. It is evident that lipocaic had no beneficial effect either in delaying the onset or in modifying the severity of the lesions (figs. 3, 4 and 5).

Table 3 presents the results of the chemical analysis of the livers in the three series of rabbits. Definite increases in cholesterol and total lipid content are produced by the oral administration of cholesterol, but this change is largely prevented by lipocaic.

COMMENT

The failure of lipocaic to prevent or to modify cholesterol-induced arteriosclerosis in rabbits in the experiments reported is doubtless of limited significance. The pancreas of each of these animals was intact, and presumably its internal secretory function was effective. It is clear that this species metabolizes cholesterol and fats with difficulty, since these substances do not ordinarily constitute a material part of the diet. However, the fact that the rise in the noncholesterol lipid fraction of the blood was entirely prevented and that the deposition of cholesterol and fats in the liver was greatly decreased proves that lipocaic is able to influence the fat metabolism of rabbits. Failure to prevent the deposition of cholesterol and lipids in the intima of the aorta might therefore be due to inadequate dosage or to the method of administration. The answers to these questions must await the development of more potent preparations of lipocaic.

CONCLUSIONS

The oral administration of cholesterol to rabbits produces sustained hyperlipemia, hypercholesteremia, arteriosclerosis of the aorta and accumulation of cholesterol and fat in excessive amounts in the liver and the adrenal glands.

The simultaneous oral administration of lipocaic in amounts up to half of that required daily by the depancreatized dog prevents a rise in the noncholesterol fraction of the blood lipids and also the deposition of fat and cholesterol in the liver but has no effect on hypercholesteremia and arteriosclerosis caused by the oral administration of cholesterol.

CONVULSIONS DURING GENERAL ANESTHESIA

REPORT OF A CASE

PAUL H. LORHAN, M.D.

KANSAS CITY, KAN.

Convulsions or violent involuntary muscular contractions which are occasionally noted in patients during anesthesia induced with ether constitute a definite clinical entity. They cause the anesthetist a great deal of anguish until they are controlled since the death of a patient during a seizure on the operating table is not rare. Lundy¹ reported a mortality rate of 18.97 per cent in a series of 144 cases. Payne² calculated the mortality rate to be 23 per cent. Woolmer and Taylor³ stated the mortality rate to be about 50 per cent. The frequency of ether convulsions is said to be between 1 in 5,000 and 1 in 10,000. Recently reports have been appearing in the literature regarding convulsions during anesthesia induced with divinyl ether.⁴

A sequela equally as tragic as death is complete loss of the mind; this occurred in Weber's⁵ case. His patient was a child of 4 years who had convulsions while he was under ether anesthesia during appendectomy.

Although much has been written on the subject since Wilson⁶ and Pinson⁷ reported the first cases in 1927, no satisfactory solution of the problem has been presented. The factors which have been suggested

From the Hixon Laboratory for Medical Research and the Department of Anesthesia, The University of Kansas School of Medicine.

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as causing or contributing to ether convulsions are legion and are frequently contradictory.

Nosworthy⁸ and Sykes⁹ mentioned that the seizures occur almost exclusively in children. Clarke¹⁰ suggested sex susceptibility, stating that the condition is more common in female patients. Toxemia and septicemia are commonly named as predisposing factors.¹¹ Rovenstine¹² considered trauma to play a part. A. J. D. Smith,¹³ Hadfield,¹⁴ Wright¹⁵ and Hewer¹⁶ expressed the opinion that elevation of temperature may be a factor. F. W. G. Smith¹⁷ stated his belief that heat stroke played an important part in Wright's¹⁸ case in which Wright was able to control the convulsions by spinal anesthesia and pentobarbital sodium. In this connection it is interesting that overdosage of atropine has generally been implicated by British anesthetists.¹⁹ Sington²⁰ questioned the influence of this factor, however, for he observed no convulsions in children over 6 years of age who received $\frac{1}{80}$ grain (0.00075 Gm.) of atropine by mouth.

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12. Rovenstine, E. A.: Convulsions During Ether Anesthesia, *Anesth. & Analg.* **14**:40 (Jan.-Feb.) 1935.

13. Smith, A. J. D.: Ether Convulsions, *Brit. M. J.* **2**:80 (July 12) 1930.

14. (a) Hadfield, C. F., in Discussion on Late Ether Convulsions, *Proc. Roy. Soc. Med. (Sect. Anaesth.)* **21**:33 (Aug.) 1928; (b) *Practical Anaesthetics for the Student and General Practitioner*, ed. 2, New York, William Wood & Company, 1931, p. 111.

15. Wright, A. D.: Ether Convulsions, *Brit. M. J.* **1**:949 (May 4) 1935.

16. Hewer, C. L.: Ether Convulsions, *Brit. M. J.* **2**:80 (July 12) 1930.

17. Smith, F. W. G.: Ether Convulsions or Heat Stroke? *Brit. M. J.* **1**:77 (Jan. 13) 1934.

18. Wright, A. D.: Nembutal in Ether Convulsions, *Brit. M. J.* **2**:1210 (Dec. 30) 1933.

19. (a) Daly, A.: Two Instances of Ether Convulsions, *Brit. J. Anaesth.* **14**:162 (July) 1937. (b) Hornabrook, R. W.: Convulsions Occurring During Surgical Anesthesia, *Brit. M. J.* **2**:471 (Sept. 10) 1927.

20. Sington, H.: Convulsions During Anaesthesia: Atropine in Childhood, *Brit. M. J.* **2**:566 (Sept. 24) 1927.

Fairlie,²¹ Pinson²², and Shipway²³ expressed the belief that the technic of administration of the anesthetic must enter into consideration of the causes of convulsions. It also has been suggested by numerous workers²⁴ that unnecessary depth of anesthesia may play a part. Laurie,²⁵ on the other hand, stated that *too light anesthesia is a more likely cause*. Hadfield^{14a} and others²⁶ mentioned the importance of impurities in the ether. They were unable to explain why ether convulsions were not reported in the literature before 1926. Rood and Webber²⁷ expressed their opinion that impurities in ether are the result of mixing old residues with fresh ether in the anesthetic machine.

That the answer to the problem may lie in the patient is a possibility which has not been overlooked. Kemp²⁸ and King²⁹ thought that some patients possess an idiosyncrasy for ether or a predisposition to convulsions. This is in itself a vague statement, and many authors³⁰ have attempted to shed light on the nature of this predisposition to ether

21. Fairlie, H. P.: Convulsions During General Anesthesia, *Brit. M. J.* **2**:897 (Nov. 12) 1927; Convulsions During Anesthesia, *ibid.* **2**:703 (Oct. 15) 1927.

22. Pinson, K. B.: Ether Convulsions, *Brit. M. J.* **2**:41 (July 5) 1930; footnote 7.

23. Shipway, F. E., in Discussion on Late Ether Convulsions, *Proc. Roy. Soc. Med. (Sect. Anaesth.)* **21**:1704 (Aug.) 1928.

24. (a) Ashworth, H. K.: Ether Convulsions, *Brit. M. J.* **1**:851 (April 20) 1933. (b) Blomfield, J.: Convulsions During General Anesthesia, *ibid.* **1**:1095 (June 20) 1931. (c) Cook, B. E.: Ether Convulsions, *ibid.* **2**:679 (Oct. 10) 1931. (d) Corfield, C.: Ether Convulsions, *ibid.* **1**:1052 (May 18) 1935. (e) Courts, A. C. S.: Ether Convulsions, *ibid.* **1**:959 (May 21) 1932. (f) Hewer, C. L.: Recent Advances in Anesthesia and Analgesia, Philadelphia, P. Blakiston's Son & Co., 1932, pp. 41 and 47. (g) Thomas, L. K., in Discussion on Late Ether Convulsions, *Proc. Roy. Soc. Med. (Sect. Anaesth.)* **21**:1705 (May 4) 1928. (h) Boyle.^{11b}

25. Laurie, W. S.: Convulsions During Surgical Anesthesia, *Brit. M. J.* **1**:1002 (June 6) 1931.

26. (a) Fairlie, H. P.: Ether Convulsions, *Brit. M. J.* **1**:1195 (June 28) 1930. (b) MacKenzie, J. S.: Convulsions During Surgical Anesthesia, *ibid.* **1**:440 (March 14) 1931. (c) Sykes, W. S.: Modern Treatment Anaesthesia, New York, W. W. Norton & Company, 1932, p. 87. (d) Walton, A. C. R.: A Note on Ether Convulsions, *Brit. M. J.* **2**:8 (July 7) 1928. (e) Wilson.^{11e} (f) Hewer.^{1e}

27. Rood, F. S., and Webber, H. N.: Anaesthesia and Anaesthetics, New York, William Wood and Company, 1930, pp. 134-135.

28. Kemp, W. N.: Unusual Complications of Surgical Anesthesia Under Ether, *Brit. J. Anaesth.* **10**:145 (July) 1933.

29. King, H. J.: Convulsions Under Ether Anesthesia, *Am. J. Surg.* **30**:182 (Oct.) 1936.

30. (a) Kemp, W. N.: Tetany During Ether Anesthesia, *Anesth. & Analg.* **12**:1 (Jan.-Feb.) 1933. (b) Sears, J. B.: Late Ether Convulsions: Report of Two Cases, *J. A. M. A.* **100**:1150 (April 15) 1933. (c) Hadfield.^{14a}

convulsions. After a study of "thymic deaths," Waldbott³¹ suggested that ether and general anesthesia may be the source of allergic anaphylactic manifestations. It appeared to McDonagh³² that the actual state of the patient's protein particles before the anesthetic is administered must play a part in the production of toxic symptoms. He based this statement on the theory that anesthetic substances act by subjecting protein particles in the plasma to sudden dehydration and then to equally sudden hydration. Hyperirritability of the nervous system has been considered as a factor by Haworth³³ and F. W. G. Smith.¹⁷ Rosenow and Tovell³⁴ attributed the convulsions to a neurotoxin or poison produced by a streptococcus, which is present in amounts which are insufficient to cause spasms but which in the presence of general anesthesia are sufficient to initiate convulsions. Lundy¹ stated that this offers the most promising explanation. Mousel³⁵ reported convulsions occurring in a child who had a neurotropic strain of streptococcus in the throat. The child was anesthetized again two weeks later. At this time cultures yielded no growth, and the anesthesia was uneventful.

Haworth³⁶ considered cerebral anemia as a factor and reported cessation of convulsions in a case after the foot of the bed had been elevated. On the other hand, Clarke¹⁰ and Daly³⁷ suggested the possibility that increased vascularity of the cerebral cortex, especially of the rolandic area, may play a role. Hewer^{24f} concurred in this opinion, and Woolmer and Taylor³ thought that this increased vascularity may play a part. Jirka and Hofrichter³⁸ mentioned that some cases have been reported in which autopsy revealed a tumor of the brain, which usually showed hemorrhage as the primary cause of the convulsions.

The composition of the blood has been fairly well investigated in a search for the cause of ether convulsions. Sears^{30b} and others³⁹

31. Waldbott, G. L.: Late Ether Convulsions, *J. A. M. A.* **100**:1557 (May 13) 1933.

32. McDonagh, J. E. R.: Convulsions During General and Local Anesthesia, *Brit. M. J.* **2**:1118 (Dec. 10) 1927.

33. Haworth, J.: Convulsions During Ether Anesthesia, *Brit. M. J.* **2**:400 (Aug. 29) 1931.

34. Rosenow, E. C., and Tovell, R. M.: Etiology of Muscular Spasms During General Anesthesia, *Am. J. Surg.* **34**:474 (Dec.) 1936.

35. Mousel, L. H.: An Unusual Case of Convulsions Under Anesthesia, *Proc. Staff Meet., Mayo Clin.* **15**:33 (Jan. 17) 1940.

36. Haworth, J.: Ether Convulsions, *Brit. M. J.* **1**:1156 (June 18) 1932. Footnote 33.

37. Daly, A.: Ether Convulsion: A Note as to Treatment, *Brit. J. Anaesth.* **9**:68 (Jan.) 1932.

38. Jirka, F. J., and Hofrichter, F. C.: Convulsions Under Anesthesia with a Report of Four Cases, *Illinois M. J.* **75**:549 (June) 1939.

39. Josephs, H.: Fasting as a Cause of Convulsions, *Am. J. Dis. Child.* **31**:169 (Feb.) 1926. Wilson.^{11e}

described hypoglycemia as a cause. A disturbance of calcium metabolism has been mentioned by Hudson ⁴⁰ and Raab.⁴¹ Fraser ⁴² considered ketosis important.

Riddell ⁴³ and Corfield ^{21d} thought that the convulsions were due to giving oxygen with ether. Mennell ⁴⁴ suggested hyperoxygenation as the primary factor, but Sapwell ⁴⁵ and McDonald ⁴⁶ denied this as a possibility. Smith ¹³ considered impurities in the oxygen to have some importance.

Gwathmey,⁴⁷ Clement ⁴⁸ and Schreiber ⁴⁹ expressed the opinion that anoxia is the cause, and Guedel ⁵⁰ said that if anoxia is a factor, it is of the histotoxic type. Bradshaw ⁵¹ reported a case in which determinations of the blood oxygen were made; he found the oxygen capacity decreased to 14.6 volumes per cent and the oxygen saturation to 47.3 per cent. A. J. D. Smith ¹³ stated that if analyses for oxygen had been made in cases of ether convulsions a clue to the cause might have been found. Hoseason ⁵² stated his belief that it is possible for lack of oxygen to play a part, even though the blood may be fully saturated with oxygen, if owing to the low carbon dioxide tension the dissociation of oxygen is inhibited. In discussing the signs and symptoms suggestive of lack of oxygen, Waters ⁵³ mentioned muscle twitchings and contractions as a sign prone to occur in the operating room. Bailey ⁵⁴ reported 2 cases in which patients with convulsions occurring during ether anesthesia showed definite signs of a respiratory depression.

40. Hudson, R. V.: The Cause and Prevention of "So-Called" Ether Convulsions, *Brit. J. Anaesth.* **13**:148 (July) 1936.

41. Raab, A.: Convulsions During Ether Anesthesia, *Anesth. & Analg.* **15**:295 (Nov.-Dec.) 1936.

42. Fraser, L.: Convulsions During Surgical Anesthesia, *Brit. M. J.* **1**:562 (March 28) 1931.

43. Riddell, L. A.: Ether Convulsions, *Brit. M. J.* **2**:834 (Nov. 3) 1934.

44. Mennell, Z., in Discussion on Late Ether Convulsions, *Proc. Roy. Soc. Med. (Sect. Anaesth.)* **21**:39 (Aug.) 1928.

45. Sapwell, J. I.: Ether Convulsions, *Brit. M. J.* **2**:42 (July 5) 1930.

46. McDonald, N., in Discussion on Late Ether Convulsions, *Proc. Roy. Soc. Med. (Sect. Anaesth.)* **21**:40 (Aug.) 1928.

47. Gwathmey, J. T.: Ether Convulsions, *Lancet* **1**:1369 (June 25) 1927.

48. Clement, F. W.: Convulsions During Anesthesia, *Anesth. & Analg.* **7**:72 (March-April) 1928.

49. Schreiber, F.: Cerebral Anoxia and Anesthesia, *J. Michigan M. Soc.* **38**:1050 (Dec.) 1939.

50. Guedel, A. E.: *Inhalation Anesthesia*, New York, The Macmillan Company, 1937, p. 63.

51. Bradshaw, H. H.: Impurities in Ether, *Am. J. Surg.* **45**:511 (Sept.) 1939.

52. Hoseason, A. S.: Ether Convulsions, *Brit. J. Anaesth.* **13**:142 (July) 1936.

53. Waters, R. M.: Anoxia: The Anesthetist's Point of View, *J. A. M. A.* **115**:1687 (Nov. 16) 1940.

54. Bailey, H.: Ether Convulsions, *Brit. M. J.* **1**:222 (Aug. 17) 1940.

That a lack of carbon dioxide is a possible cause has been considered by Kemp.⁵⁵ Collip and Backus⁵⁵ and Kemp⁵⁶ also suggested a deficit of carbon dioxide and alkalosis as the responsible factors. On the other hand, Bashall^{11a} and others⁵⁷ considered accumulation of carbon dioxide as a cause. Overbreathing was mentioned by Grant and Goldman,⁵⁸ and Courts^{24e} asked whether hyperventilation might not play a part.

Finally, Cassels, Becker and Seevers⁵⁹ held the opinion that pyrexia and numerous other factors, particularly those which produce metabolic acidosis, increase cerebral irritability to such a level that respiratory acidosis rapidly induced, whether from respiratory depression, rebreathing or the administration of carbon dioxide, serves as an adequate stimulus to induce convulsions during anesthesia. It is possible that no single cause in the foregoing list is alone responsible for these convulsions, but that, as Cassels, Becker and Seevers⁵⁹ and Mousel⁶⁰ suggested, the convulsions may result from the interaction of two or more abnormal factors.

Although authorities differ widely regarding causation, they are in singular agreement as to the clinical picture. The patient is usually an infant or a young child; rarely, a young adult. Generally the patient is suffering from acute infection with moderate elevation of temperature. Ether is most frequently the anesthetic, although a few cases have been reported in which divinyl ether was used. Induction may be simple or difficult. One of the first untoward signs is a rapid increase in the respiration; this tends to become labored as anesthesia progresses. The first definite sign, however, is twitching about the face, usually beginning above the eyes. The pupils at this time will be widely dilated, inactive to light, with the eye centrally fixed. The twitching then spreads to the facial, neck and shoulder muscles, from here to the arms and the abdomen and finally to the legs. As the spasm spreads, it becomes more violent and sustained. The convulsions are both clonic and tonic and may become so severe that operation is impossible.

55. Collip, J. B., and Backus, P. L.: The Effect of Prolonged Hyperpnœa on the Carbon Dioxide Combining Power of the Plasma, *Am. J. Physiol.* **51**:568 (April) 1920.

56. Kemp (footnotes 28 and 30 a).

57. (a) Bull, L. J. F.: Convulsions Occurring During Surgical Anesthesia, *Brit. M. J.* **2**:471 (Sept. 10) 1927. (b) Dickson, D. C.: Convulsions During Anesthesia, *ibid.* **2**:613 (Oct. 1) 1927. (c) Pinson, K. B.: General Convulsion Under Ether, *ibid.* **2**:277 (Aug. 10) 1929. (d) Footnote 7.

58. Grant, S. B., and Goldman, A.: A Study of Forced Respiration, *Am. J. Physiol.* **52**:209 (June) 1920.

59. Cassels, W. H.; Becker, T. J., and Seevers, M. H.: Convulsions During Anesthesia, *Anesthesiology* **1**:56 (July) 1940.

60. Mousel, L. H.: Ether Convulsions, *Proc. Staff Meet., Mayo Clin.* **14**: 285 (May 3) 1939.

Previous to the violent contractions, the color is usually good; but as the seizures continue, cyanosis of varying degree sets in. Hypersecretion of mucus is a prominent feature and necessitates suction to keep the airway patent. The temperature rises to as high as 105 or 107 F. In the cases in which death occurs immediately, respiration ceases after five or fifteen minutes, and deep cyanosis develops. The heart will stop after a short interval. The primary convulsive seizures may disappear, but the patient may fail to recover consciousness on return to his room. At this time the urine is usually strongly acid and may contain casts, albumin and acetone.⁶⁰ Death may occur later with bronchopneumonia as the immediate cause. Dramatic recovery may ensue, even in the most severe cases, but transient or permanent mental disorders may result.

These convulsions are not to be confused with the muscular twitchings which occur during the induction of anesthesia with a mixture of nitrous oxide and oxygen and which subside as soon as the oxygen is increased. During the induction of anesthesia with ether, one frequently observes clonic spasms of the legs and arms; however, these usually last for only a short time. These also differ from the true ether convulsions, which occur only after onset of surgical anesthesia and frequently not until the end of the operation.

The pathologic nature of ether convulsions is not definitely known since few autopsies have been reported. No gross lesion suggesting a cause for the convulsions appears to have been observed. F. W. G. Smith^{60a} stated that extreme cerebral congestions occur and that edema of parts of the lungs is a common finding. In the case reported by Schnedorf, Lorhan and Orr⁶¹ these same gross changes were present, but histologically, cerebral anoxic changes were observed.

The treatments advocated for ether convulsions are as numerous as the theories advanced for their cause. It is generally agreed, however, that time is a major factor in establishing a favorable prognosis. Wilson¹¹⁶ recommended the use of 50 per cent dextrose intravenously. Raab⁴¹ and Hoseason⁵² advised the intravenous injection of 10 cc. of a solution of calcium gluconate followed by a solution of dextrose. Lundy¹ suggested that the convulsions can usually be controlled by the use of a barbiturate intravenously. Rosenow and Tovell³⁴ concurred in this opinion. Dodd⁶² has used evipan (sodium salt of *n*-methyl-C-C-cyclohexamyl-methyl barbituric acid); and Daly¹⁹ suggested that this is

60a. Smith, F. W. G.: Late Ether Convulsions, Irish J. M. Sc., September 1936, p. 577.

61. Schnedorf, J. G.; Lorhan, P. H., and Orr, T. G.: Problem of Anoxia in Surgical Anesthesia: Report of Experimental and Clinical Cases and Review of the Literature, Arch. Surg. **43**:169 (Aug.) 1941.

62. Dodd, H. G.: Ether Convulsions Controlled by Evipan, Brit. J. Anaesth. **14**:167 (July) 1937.

probably the safest treatment if all others fail. Chadwick⁶³ stated his belief that evipan is more satisfactory in children than pentobarbital sodium, which requires accurate dosage and slow rate of administration. Cook⁶⁴ used pentothal sodium for the control of convulsions. Wyatt⁶⁵ outlined a definite program for combating this clinical syndrome as follows: (1) A soluble barbiturate should be at hand whenever a child is to be operated on for an acute septic process; (2) chloroform, oxygen and carbon dioxide should be readily available; (3) a solution of calcium gluconate or a 50 per cent solution of dextrose for intravenous use should be provided. Hoseason⁵² recommended the administration of a calcium compound or the intravenous injection of any hypertonic solution. Lundy¹ stated that as to the selection of anesthesia in cases of profound toxemia it might be better to use spinal, infiltration or block anesthesia or to use avertin with anylene hydrate to produce basal anesthesia rather than to use only an inhalation anesthetic. Laurie²⁵ also stated his preference for spinal rather than general ether anesthesia. Wilson,¹¹⁶ however, expressed the view that in the majority of cases ether convulsions can be prevented by the administration of dextrose in a solution of sodium chloride preoperatively to toxemic patients. A suggested outline of treatment would comprise the following essentials: (1) careful selection of anesthesia for the acutely ill toxic patient, with spinal or basal anesthesia the anesthesia of choice; (2) administration of dextrose in a solution of sodium chloride before operation; (3) moderate dosage of depressant drugs; (4) administration of oxygen; (5) intravenous use of a barbiturate, preferably evipan if convulsions develop; (6) keeping the airway patent; (7) cessation of operation until convulsions are under control.

REPORT OF CASE

The patient was a boy, aged 14 years and weighing 190 pounds (86.2 Kg.). At birth he weighed 16½ pounds (7.3 Kg.), and forceps were required for delivery. As a result Erb's paralysis of the right side developed. The past history was essentially noncontributory except for frequent colds and fevers. On admission to the hospital, the patient had a temperature of 101 F., a pulse rate of 86 and a respiration rate of 22; the blood pressure was 128 systolic and 70 diastolic. A diagnosis of acute appendicitis was made. One fourth of a grain (0.016 Gm.) of morphine sulfate with ⅓₁₅₀ grain (0.0004 Gm.) of atropine sulfate was given at 6:40 a. m. as preliminary medication.

63. Chadwick, T. H.: Evipan Sodium Treatment of Ether Convulsions, *Brit. M. J.* 1:1252 (June 20) 1936.

64. Cook, W. B.: Convulsions Associated with Nitrous-Oxide-Ether Anesthesia, *Northwest Med.* 39:182 (May) 1940.

65. Wyatt, O. S.: Convulsions in Children While Under Ether Anesthesia, *Minnesota Med.* 23:101 (Feb.) 1940.

Anesthesia induced by nitrous oxide, oxygen and ether was started at 7:42 a. m., and the operation was begun at 7:55. Up to this time 40 cc. of ether had been given; the carbon dioxide absorption technic was used with a pharyngeal airway in place. The respiration at this time was quiet and regular at a rate of 32. The pulse rate was 72. The peritoneum was opened at 8:05. Shortly after this the pupils dilated, and the breathing became stertorous and labored. Anesthesia was lightened with improvement of the respiration and the general condition of the patient. At this time the surgeon requested deeper anesthesia because of the patient's muscular rigidity. Relaxation was obtained by giving more ether, and the appendix was delivered. The respirations again became labored and rapid, and the pulse rate rose to 120 but remained of fair quality. At 8:30, twitchings of the forehead were noted, and there was profuse frothing at the mouth. Oxygen and calcium gluconate were given at 8:43; this controlled the convulsions so that the peritoneum and the fascia could be closed. At 8:45, a second series of convulsions began, and the patient became markedly cyanotic with an irregular pulse. Calcium gluconate, coramine (a 25 per cent solution of pyridine betacarboxylic acid diethylamide) and oxygen were given without result. Evipan sodium (3 cc. of a 10 per cent solution) was given intravenously. Immediately, the convulsions began to lessen in severity, and when 4 cc. had been given, the respirations became quiet, the convulsions stopped, and the color began to improve. At 9:05, the convulsions were under control; the pulse rate was 140, the color was fair, and the skin was moist and warm. The rectal temperature at this time was 104.6 F. The patient was returned to his room in fair condition. Late in the afternoon of the same day, the temperature was 102.6 F., the pulse rate was 124, and the respiration rate was 24. The urine was alkaline, and acetone was strongly present on the breath; this was determined by the method of Roth,⁶⁶ the use of which for surgical patients has been reported by Lorhan.⁶⁷ The patient was restless for the remainder of the day and at times delirious. He also had hallucinations. The following day he had severe headache and marked diarrhea; however, both of these yielded to treatment. Later convalescence was uneventful.

COMMENT

The following discussion is concerned with showing the relation between ether convulsions and cerebral anoxia. In this case toxemia was present with a slight elevation of temperature. One fourth of a grain (0.016 Gm.) of morphine as premedication was probably too much, for McClure, Hartman, Schnedorf and Schelling⁶⁸ found that narcotics, and particularly morphine, tend to produce anoxia of the histotoxic type. With the administration of $\frac{1}{150}$ grain (0.0004 Gm.)

66. Roth, P.: Scope and Utility of Tests for Carbon Dioxide Tension and Acetone in Alveolar Air in Relation to Surgery and Anesthesia, *Anesth. & Analg.* 6:266 (Dec.) 1927.

67. Lorhan, P. H.: Determinations of Acetone in Expired Air: Its Value in Anesthesia and the Surgical Patient, *Anesth. & Analg.* 17:316 (Nov.-Dec.) 1938.

68. McClure, R. D.; Hartman, F.; Schnedorf, J. G., and Schelling, V.: Anoxia: A Source of Possible Complications in Surgical Anesthesia, *Ann. Surg.* 110:835 (Nov.) 1939.

of atropine, a moderate dose for a patient 14 years of age, hyperthermia may have occurred. There is complete agreement⁶⁹ that atropine can play a large part in the retention of heat in the body. Guedel⁵⁰ stated that for each degree of fever the metabolic rate is increased about 7.5 per cent. With this increase of temperature there occurs an increase in metabolism, and the oxygen requirement is greater.

Ether anesthesia is known to increase the rate and the depth of respiration and then the respiratory exchange⁷⁰ Haldane⁷¹ found that these changes lower the alveolar oxygen tension, thus decreasing the oxygen saturation of the blood. This varies as a rule with the depth of anesthesia. Ether itself induces histotoxic anoxia.⁷² Shaw, Steele and Lamb⁷³ found ether to decrease the saturation of the arterial blood with an increase of its oxygen capacity. Their findings indicated the existence of anoxic anoxia in subjects under ether anesthesia. The stertorous and labored respirations and the excessive mucus present constitute a mechanical hindrance to the diffusion of oxygen from the inspired anesthetic atmosphere into the blood. This, combined with the presence of fluid in the alveoli, contributes also to anoxic anoxia owing to the delivery of insufficient oxygen to the blood by the lungs.

Postoperatively, the patient showed signs of cerebral oxygen want as described by Waters,⁵³ indicated by headache, restlessness, delirium and anxiety. Hewitt⁷⁴ mentioned that hallucinations may occur in patients who have been subjected to want of oxygen to various degrees. This discussion does not pretend to demonstrate the cause of ether convulsions but rather the part that cerebral oxygen want may have played in the production of convulsions in the patient described. The presence of a strain of streptococci which might have induced sensitiveness to ether has not been ruled out in this case. Oxygen studies were not made but the clinical picture is a sufficient basis for the diagnosis of cerebral oxygen want.

From the foregoing discussion it is plausible that cerebral oxygen want may have developed in this patient at some time during the induction or the maintenance of surgical anesthesia. Careful analysis of the

69. Bastedo, W. A.: *Materia Medica, Pharmacology, Therapeutics and Prescription Writing*, ed. 4, Philadelphia, W. B. Saunders Company, 1937, p. 510.

70. Embley, E. H.: *The Action of Ether upon the Circulation*, *J. Biochem.* 5:79, 1910.

71. Haldane, J. S.: *Symptoms, Causes and Prevention of Anoxemia and the Value of Oxygen in Its Treatment*, *Brit. M. J.* 2:65 (July 19) 1919.

72. Brow, G. R., and Long, C. N. H.: *Biochemical Changes in the Heart Muscle During Anesthesia*, *Anesth. & Analg.* 9:193 (Jan.-Feb.) 1930.

73. Shaw, J. L.; Steele, B. F., and Lamb, C. A.: *Effect of Anesthesia on Blood Oxygen*, *Arch. Surg.* 35:1 (July) 1937.

74. Hewitt, F. W.: *Anaesthetics and Their Administration*, ed. 5, London, Oxford University Press, 1922, pp. 120 and 246.

case will show: (1) that this patient had a slight elevation of temperature which increased his oxygen demand; (2) depressing preoperative medication decreased the oxygen saturation of the blood and resulted in anoxia; (3) asphyxia incident to induction of anesthesia with a mixture of nitrous oxide and oxygen produced anoxic anoxia; (4) the mechanical hindrance incident to the stertorous and labored respirations as well as the excessive mucus which was present during the seizure contributed to the anoxia. These factors combine with the anoxia of ether anesthesia to produce the dread clinical picture of ether convulsions.

SUMMARY

A case of ether convulsions in a 14 year old white boy is here recorded.

The etiology of ether convulsions is discussed. No uniformity of opinion concerning the causative factor or factors was found in the literature.

Descriptions of treatment in the literature are indefinite and inconclusive; however, the majority of authors agree that a barbiturate, preferably evipan, should be given.

The choice of anesthesia is debatable, but the spinal, regional and infiltration types seem to be the safest for patients with toxemia.

The factors producing oxygen have been discussed as possible causes of ether convulsions.

Finally, as a solution to the problem has not been found, the anesthetist should be constantly on the alert so that the condition may be recognized early and treatment instituted immediately if this appalling mortality is to be reduced.

LARGE SOLITARY CYSTS OF THE KIDNEY

TYPES, DIFFERENTIAL DIAGNOSIS AND SURGICAL TREATMENT

ROBERT GUTIERREZ, M.D.

NEW YORK

No comprehensive clinicoanatomopathologic classification of renal cysts has been published, so far as I have been able to discover. There was formerly much confusion with reference to large solitary serous cyst and polycystic disease of the kidneys, both as to their pathogenesis and as to their clinical manifestations. Especially has there been difficulty in differentiating preoperatively between large serous cyst and hemorrhagic cyst of the kidney and between both of these and neoplastic tumor. Accordingly it seems desirable to present such a classification with a view to promoting a better understanding of these cystic formations, the origin of which has been shrouded in obscurity and the differentiation of which is still attended with so much difficulty. In fact, only since the arrival of modern methods of roentgenographic and urographic examination has it been possible to make a preoperative diagnosis with reasonable assurance and to differentiate large serous cyst of the kidney from solid tumor of this organ or of the neighboring viscera.

I wish to emphasize the feasibility and the importance of recognizing before operation not only the presence of a renal cyst, but also the type of such a cyst and its location, size and nature, as well as the best avenue of approach, since on this recognition must depend the prognosis and the form of operative treatment that is appropriate in each case. In the past most cases of large serous cyst of the kidney were not preoperatively diagnosed; the cyst was usually discovered in the course of laparotomy, naturally to the detriment of the patient, or was diagnosed at autopsy.

Today, the finding of such a cyst is no longer a rarity, and the approach to the cyst by a logical route determined in advance of operation has become surgically possible. On the basis of 10 cases hereinafter reported, I have undertaken to review the principal points to be considered in differential diagnosis and to point out the considerations that must govern the choice of an operation, since the surgical procedure will be conservative or radical, according to the type of case in question.

Read at the thirty-eighth annual meeting of the American Urological Association, Colorado Springs, Colo., May 21, 1941.

It must be emphasized, however, that in most cases the cyst can be treated conservatively. As a rule the sacrifice of a kidney is not necessary or justifiable and is to be considered only in those exceptional cases in which the cyst is associated with complications that render nephrectomy inevitable.

HISTORY AND LITERATURE

The large serous cyst of the kidney has long been known and has been recorded in ancient works on pathology, but no definite account of its clinical history has appeared until relatively recent times. Renal cysts were described by Fabricius of Hilden, known as the Father of Germany Surgery, who died in 1634. In the same century the famous English clinician Thomas Willis made some allusions to cystic formations within the kidney but made no clear differentiation of types. In 1833, Hawkins gave a detailed account of an "encysted serous tumor of the kidney" in a small boy 6 years of age treated in the service of one Dr. Seymour by the administration of "calomel, castor oil, leeches and an ointment consisting of iodine and mercury in equal parts, combined with repeated puncture, notwithstanding which the child died."

Isolated cases of serous or blood cyst of the kidney were reported by Hare (1850), Lancereaux (1858), Thomson (1861), Campbell (1874), Virchow (1869) and Laveran (1876). Virchow suggested that this type was the result of papillary inflammatory obstruction during intrauterine life. In 1874, Campbell did the first successful nephrectomy in such a case. Lancereaux distinguished between serous and hemorrhagic cysts, while Laveran was the first to differentiate large solitary cyst from polycystic disease of the kidney. In 1865 Touren presented a thesis in which he reported several cases of large serous cyst.

Not until 1906 was any comprehensive research done on the subject, when Simon discussed in a thesis 52 cases which he had collected from the literature. In 1911, Brin removed some doubtful cases from among these and replaced them with others more reliable, bringing the number to 53. By 1925, 120 cases had been collected by Laquière; Kretschmer brought the figure to 150 in 1930, and Stirling, in 1931, found 230 cases on record. Finally, in 1932, Simkow, in a thesis, reported on his collection of 315 cases of large serous cyst of the kidney, but many more cases have since been reported, indicating that the condition is not as rare as was formerly believed. Speaking in terms of percentage, Branch stated in 1929 that pathologists see these large renal cysts in from 3 to 5 per cent of routine autopsies.

Within the last two decades the causation and the embryology of these cysts have been investigated by a number of writers, among whom may be especially mentioned Rayer, Le Dentu, Küster, Caulk, Hepler

and Kampmeier. With reference to the difficulties of diagnosis, contributions have been presented by Wulff, Vogel, Fowler, Schulman, Giuliani, Lipskeroff, Cunningham, Chiasserini, Cassioli, Herbst, Higgins, Quinby and others. Modes of treatment have been discussed by Albarran and Imbert, Lejars, Tuffier, Clute, Judd and Simon, Kretschmer, Barney, Colston, Kirwin, O'Connor, Fish and many others.

CLASSIFICATION

As may be seen in table 1, cysts of the kidney fall into three main groups:

The first group consists of the multiple minute cysts commonly found in kidneys of patients with chronic nephritis or even in normal kidneys. These are of no clinical or surgical significance and will not be discussed here.

In the second group are the cysts found in polycystic kidneys, which likewise are not dealt with in this paper. Polycystic disease of the kidney is overwhelmingly bilateral, but in rare instances it has been found to be present in only one of the kidneys, while the other was normal. Polycystic disease of the kidneys, always congenital, may be accompanied by any other type of associated pathologic change and has been discussed exhaustively in the literature by a great many authors.

In the third group are the large solitary serous cysts, which constitute the subject of this paper. Although termed solitary to distinguish them from the cysts of polycystic kidneys, serous cysts may not in fact be single, since it is not uncommon to find one large cyst, outstanding by reason of its size, accompanied by one or several smaller cysts. But, because of the relative insignificance of these smaller sacs and because they do not form groups and do not become fused but remain separated by sound portions of renal parenchyma, the term "solitary" continues to be appropriate. Usually, however, cystic formations of the type in question are now spoken of as "large serous cyst of the kidney," even though the size of the large cyst may not exceed that of a walnut. The finding is usually a large simple cyst, filled with serous fluid which occasionally becomes hemorrhagic, and in some cases it attains a great size, filling the entire abdominal cavity.

With reference to origin, cysts of this type may be divided in general into those that are congenital and those that are acquired. However, as will be seen when the causation is discussed, it is an open question whether there is not in every case an embryonic base for the cyst's development, constituting the soil on which some trauma or other cause acts at a later period to bring the cyst into manifestation from what was previously only a state of potentiality. Nevertheless, from the fact that

in the majority of cases there is no sign of the existence of such a cyst until maturity has been reached, i. e., between the ages of 30 and 70, one is justified in assuming that some of these cysts may properly be classi-

TABLE 1.—Classification of Cysts of the Kidney

Multiple minute cysts of nephritis			
Polycystic kidney disease			
Solitary cysts	Congenital	{ Unilateral	
		{ Bilateral	
	Acquired	{ Unilateral	
		{ Bilateral	
Large solitary cysts of the kidney	According to number	{ Unilocular	
		{ Bilocular	
		{ Multilocular	
	According to size	{ Small	
		{ Large	
		{ Voluminous	
	According to location	{ Upper pole	
		{ Lower pole	
		Intrarenal	{ Anterior
			{ Posterior
		{ Convex border	
		In anomalous kidney	{ In isthmus of horseshoe kidney
			{ In hydronephrosis
			{ In aplastic kidney
			{ In double kidney
			{ In ectopic kidney
		Perinephric.....	{ Between the two layers of renal capsule
			{ Between kidney and its fibrous renal capsule
		Pararenal.....	{ Pararenal pelvic cysts
			{ In embryonic wolffian or müllerian ducts
			{ In teratoma
			{ In fatty capsule
			{ In lymphatic tissue
			{ In neurologic tissue
			{ In perirenal hematoma from ruptured kidney
		In other neighboring organs	{ Adrenal
			{ Liver
			{ Pancreas
		According to type of lesion	{ Spleen
			{ Ovaries
			{ Omentum
			{ Serous
			{ Hemorrhagic
			{ Purulent
			{ Containing a tumor
		According to type of lesion	{ Calcified
			{ Hydatid
			{ Dermoid
			{ Tuberculous
			{ Simple thin-walled cyst containing serous fluid and arising from renal parenchyma with no pyelic connection
			{ Cyst connected with a calix or with the renal pelvis
			{ Extrarenal or pararenal cysts

fied as acquired. On the other hand, the finding of such a cyst in an infant a few weeks of age clearly indicates congenital origin.

The number of pockets in the large serous cyst is subject to some variation, for it is found as unilocular, bilocular or multilocular. In all cases the cavity is traversed by walls, complete or incomplete, which may

subdivide it into separate pockets or may leave it with intercommunicating chambers partially separated by septums.

The size of the large serous cyst varies through a wide gamut, running from that of a walnut to that of an orange or grapefruit in the average case but attaining in exceptional cases such voluminous dimensions that the entire abdominal cavity is occupied by the cystic sac, causing the other viscera to be crowded out of their natural position and thereby to suffer great detriment. The cyst may accordingly be known as small, large or voluminous. In 1 of 2 cases in which operation was performed by Kelly, the cyst contained 2,300 cc. of blood-stained fluid; in the other, 1,000 cc. of clear serous fluid.

As to location, the large serous cyst of the kidney may be found at the upper or the lower pole of the kidney, on its convex border, within the kidney parenchyma, on the posterior or the anterior surface, at the internal border or at the hilus (fig. 1 *A*). In Simkow's series the cyst was at the lower pole in 78 cases and at the upper pole in 39; on the anterior surface in 11 and on the posterior in 3. In a case of Hertz the cyst occupied both poles simultaneously. There have been other cases in which the cyst was pyelorenal.

Not infrequently solitary serous cyst is found in an anomalous kidney, as for example, in a horseshoe kidney, in which it has been observed occupying the isthmus, as in Moynihan's case, or in one or the other portion of the double organ. Aplastic kidney, double kidney and ectopic kidney have all been found associated with solitary serous cyst.

A cyst developing at the expense of the kidney may be perinephric, pararenal or even within some other neighboring organ. The perinephric cyst may lie between the two layers of the renal capsule, between the kidney and the fibrous capsule or within the kidney parenchyma close to the renal pelvis but not opening into the latter. The pararenal cyst may be encountered within an embryonic wolffian or müllerian duct, or in a teratoma; it may lie within the fatty capsule of the kidney or within the renal lymphatic tissue, or it may develop in a perirenal hematoma from a ruptured kidney.

The large serous cyst of renal origin may be met with likewise in the adrenal glands, the liver, the pancreas, the spleen, the ovaries, the omentum or other neighboring viscera on which it has encroached in the course of its development. It is present in some cases of hydro-nephrosis but exists independent of the latter.

A cyst that begins as a simple serous cyst of the kidney may in the course of its development undergo changes that affect its type (fig. 1 *B*). It may thus become a hemorrhagic cyst if rupture of a vessel occurs within its wall: infection may cause it to become a purulent cyst; within

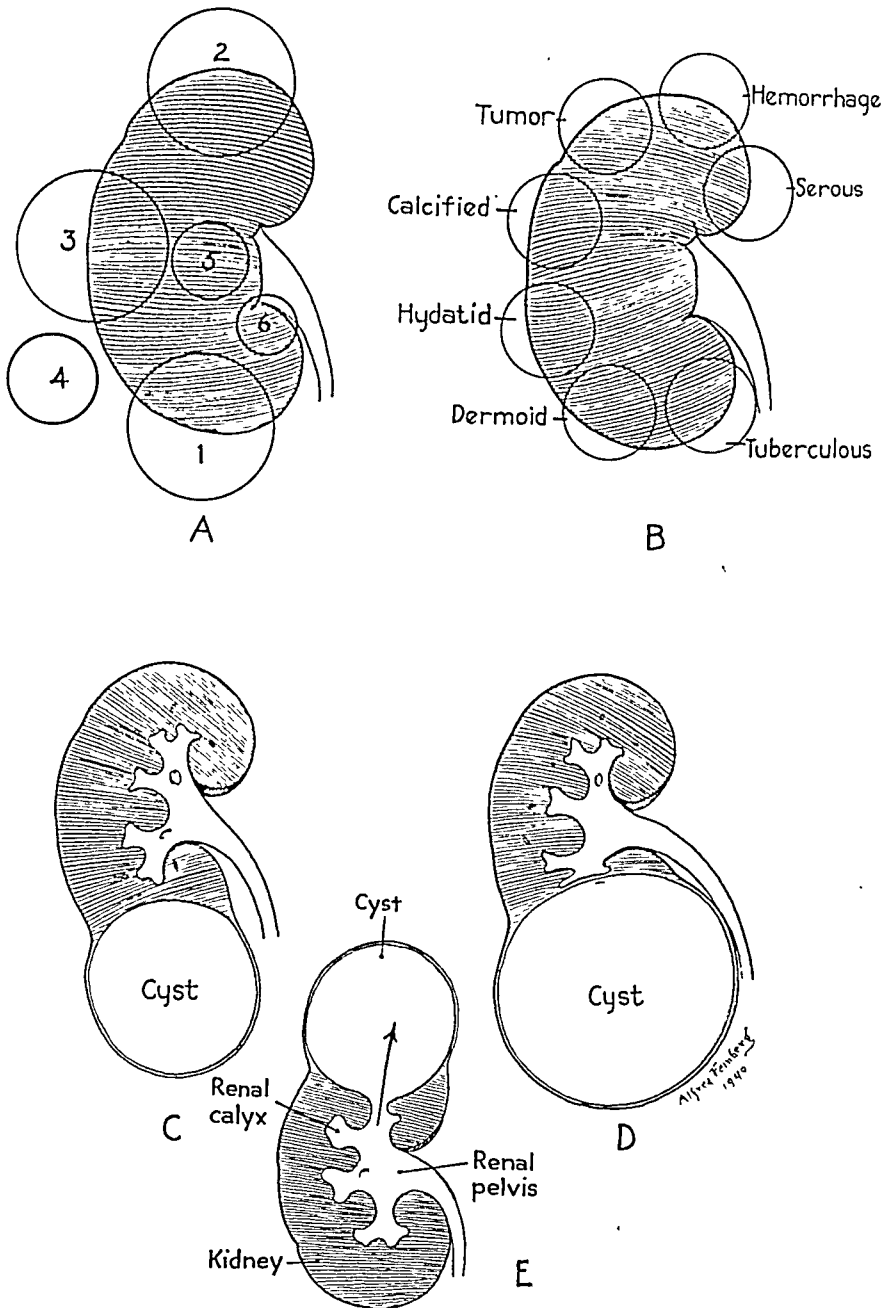


Fig. 1.—Classification and clinical types of large solitary cyst of the kidney. *A* represents the order of frequency with reference to anatomic position: 1, the lower pole; 2, the upper pole; 3, the external border; 4, pararenal site; 5, intra-renal site; 6, pyelorenal site. *B* represents the types most commonly found in order of frequency; large serous cyst, hemorrhagic cyst, cyst containing a tumor, calcified cyst, hydatid cyst, dermoid cyst and tuberculous cyst. *C* illustrates a sagittal view of the kidney with a cyst of the lower pole lying within the parenchyma but having no pyelic connection with the excretory apparatus of the kidney. *D* shows another type, in which there is a larger cyst at the lower pole of the kidney, compressing the lower calyx and displacing the ureter but still not opening into either the calix or the renal pelvis. *E* illustrates the large single cyst at the upper pole of the kidney connected with the upper calix.

its contour there may arise a true neoplastic tumor masking the diagnosis; frequently such a cyst may become calcified or may contain a calculus or calculi; more rarely a combination of lesions may be present in the cystic kidney. Hydatid, or echinococcic, dermoid and tuberculous cysts have all been found in the group of serous cysts of the kidney.

When a cyst is within the kidney structure, it may or may not have a connection with a calix or the renal pelvis. Such a connection is rare in a large simple serous cyst of the kidney. Even when the cyst is of considerable size and by compression has destroyed a substantial amount of renal parenchyma, no connection is the rule (figs. 1 *C* and *D*). However, in cases complicated by infection or another type of associated lesion, an opening may develop which can be demonstrated urographically and anatomopathologically (fig. 1 *E*).

PATHOGENESIS

The exact cause of large serous cyst of the kidney is still unknown, although modern modes of investigation have thrown a certain amount of light on it.

Various theories have been set forth, each with some degree of plausibility. Albarran (1903) expressed the opinion that the cyst is the result of a simple variety of polycystic degeneration confined to a restricted portion of a kidney and leaving the rest of the renal parenchyma intact. He thought that a number of smaller cysts became fused together, with production of one cyst of greater or lesser size. He suggested also that since the cyst is lined with epithelium, it might be a neoplasm which has assumed a cystic character. It is now known, however, that this epithelial lining is by no means a constant finding and that when it exists it does not appear to possess any special significance.

Virchow thought the cyst was due to interstitial nephritis in intra-uterine life leading to inflammatory sclerosis and consequent occlusion of some of the uriniferous tubules with resultant formation of a retention cyst.

The theory that the cyst has its origin in an embryonic rest and developmental defect has found many adherents. A failure of the S-shaped anlagen of the uriniferous tubules to unite with the straight collecting ducts owing to some obstruction from within or without has been generally accepted. Some have held that the cyst is due to rupture of the uriniferous tubules and shedding of epithelial cells into the intercanalicular connective tissue. Rokitansky thought that it is formed by metamorphosis of the cells of the malpighian bodies. Stoppage of the canals with salts or other debris after a localized inflammatory process has obliterated a segment of the tubule or the duct has been another common hypothesis.

In 1923, Kampmeier, in an actual study of fetuses, observed the apparently constant appearance of renal cysts at a certain period of fetal life, about the end of the third or the beginning of the fourth month. He noted that normally these redundant structures degenerate but pointed out that if they fail to do so at the end of the allotted time and instead continue to grow and expand, to the detriment of other adjacent normal structures, a normal physiologic event is converted into an abnormal or pathologic condition. He considers it reasonable to assume that the renal cyst is more frequently produced by the persistence and later expansion of cystic tubules which failed to collapse during fetal life than by an occlusive process in the embryo.

In 1930, Hepler succeeded in producing renal cysts in rabbits. He noted that simple occlusion does not result in cyst formation but that there must be in addition interference with the local blood supply. He found that group tubular obstruction plus anemic degeneration causes a cyst to form. He observed the development of obliterating endarteritis with sclerosis of groups of arterioles and glomeruli resulting in nutritional disturbances of the adjoining parenchyma; the subtending tubules then atrophied with substitution of connective tissue, whereat small groups of tubules, the glomeruli of which were not involved, became occluded by peritubular sclerosis and this led to dilatation with cysts. Although the cysts were small, Hepler expressed the opinion that if larger vessels are occluded, large cysts must form. The relation of some of Hepler's experimental cysts to nephritis is undeniable; in 28 animals there were definite nephritic changes, chiefly of a vascular nature.

Caulk, who discussed the pathogenesis of the large serous cyst of the kidney at some length, held that the weight of evidence is on the side of congenital origin but that some form of obstruction in the uriniferous tubules always plays a part and causes retention. It is evident that in many cases trauma or some other acquired pathologic condition later brings the cyst into manifestation. Thus it has been pointed out that the cyst appears most frequently at the age when arteriosclerosis has set in. It seems that it grows slowly in the early period of life but that it is related in some way to the acquired renal lesions of adult life, which start it and stimulate it to rapid growth in the middle and later years of life. The most common form of obstruction is localized inflammation with peritubular sclerosis and contraction leading to retention.

It has not escaped notice that congenital renal anomalies are frequently the site of cystic formations. Cyst associated with supernumerary kidney, congenital solitary kidney, ectopic kidney and horse-shoe kidney have all been reported as not infrequent.

Haslinger thought that in view of the widely different localizations of the large serous cyst of the kidney it must be concluded that the

pathogenesis is not the same in all cases. Pousson shared this view and expressed the belief that the cyst arises from multiple causes and cannot be attributed to any single uniform origin. At all events, it seems certain that both congenital and acquired factors are at work in most of the cases.

SYMPTOMATOLOGY

In most cases, solitary cyst of the kidney gives no symptoms until the cyst attains a sufficient size to exert pressure on other abdominal organs. It is especially worthy of note that urinary symptoms are commonly absent for a long time. The most that the patient feels is a vague sense of fulness in the abdomen or of heaviness on the side chiefly affected. As the cyst continues to grow, there may be pain in the costo-vertebral angle or in the lumbar or the lower dorsal region. The pain may be indefinite and dull, or there may be attacks of more or less acute distress, which subside only to return at a later time. The pains may radiate into the lower extremities, the ureter or the testis. Laquière's patient had such acute pains in her back that constant administration of morphine was necessary, and the pains were of such a nature that a diagnosis of Pott's disease was made. Hofer had a case in which the pressure of the cyst occluded the common bile duct and also caused anuria. When the cyst is at the upper pole of the right kidney the renal symptoms are often masked by those of the liver and the gallbladder. Gastrointestinal symptoms are frequently the dominant manifestations and may be the only ones. Nausea, vomiting and even intermittent occlusion of the descending colon may be present. Since the cyst, except in rare cases, does not open into the renal pelvis or calices but remains outside of the excretory system of the kidney, it is usual to find no symptoms referable to that organ; this accounts for the infrequency with which the correct diagnosis has been made in the past before the use of pyelography and roentgenography was general. However, when the cyst is large or appropriately located, it may compress the urinary passages and cause symptoms within the urinary system. Hydro-nephrosis and pyonephrosis due to such compression of the ureter have frequently been observed. Hematuria with no other assignable cause than a serous cyst is not infrequent. Renal ptosis is present in a substantial number of cases. More frequently, however, these cysts do not suggest a renal origin; cystoscopy reveals nothing, and renal functional tests and catheterization show an unimpaired kidney and renal pelvis. On palpation, however, a fluctuant mass with smooth contour may be felt beneath the anterior wall of the abdomen projecting toward the ribs and dull to percussion. The mass is insensitive to pressure and exhibits a striking mobility, especially when renal ptosis is present and the mass is at the lower pole or external border of the kidney.

According, then, to the location and the size of the cyst, the symptoms will vary with the case, producing in extreme development weakness, secondary anemia and emaciation, with profound repercussion on the general state of health. If the cyst is in the upper pole of the kidney and if its size and weight are considerable, it will push the kidney downward and may give rise to the entire gamut of symptoms observed in cases of nephroptosis or in an ordinary case of renal tumor, pyelitis or pyelonephritis. If hemorrhage occurs or if infection is superimposed, the systemic symptoms will be severe. Smaller cysts, however, may give no symptoms whatever and may be discovered only by accident at roentgen examination or at autopsy.

PATHOLOGY

Unlike polycystic disease of the kidneys, the presence of a large serous cyst within the renal organ is usually unilateral, with the other kidney normal. Opinions differ as to whether the cyst takes its origin from the cortical or the medullary substance. Regardless of origin, however, it involves the cortex. A cyst at the upper pole will be more likely to produce pressure changes, dragging the kidney down and compressing the ureter, resulting in pyelectasis. A cyst in the lower pole, on the other hand, frequently produces hydronephrosis. According to Terrier, in 6 out of 7 cases the cyst is at the upper pole, and in 1 in 7, at the lower. Simon, however, with a series of 52 cases, found the cyst at the lower pole in 18 cases and at the upper in only 8; in other cases it was in various parts of the organ. The size, as already mentioned, is variable, but most frequently it is about that of an orange. In many cases in which the cyst cannot be removed, the size can be estimated only by the amount of fluid it contains, which in extreme cases may reach as much as 16 liters (case of Goency). The shape is spheroid or ovoid, and the contour is smooth.

As the cyst increases in size, it displaces the renal parenchyma, in which it digs, as it were, a bed for itself; it creates a corresponding depression in the parenchyma, which thereby tends to become more or less atrophied for a certain depth, below which it remains normal. Where the cyst encroaches on the parenchyma, slight chronic inflammation may be met with fatty infiltration, also slight, in the uriniferous tubules. Otherwise the kidney itself remains normal in uncomplicated cases.

The wall of the cyst is thin, fibrous and transparent; its color is whitish blue or yellowish, according to its content. It is traversed by a great number of vessels, the rupture of any one of which may cause the content of the cyst to present a hemorrhagic appearance. The thinness of the wall of the serous cyst, however, distinguishes it from the true hemorrhagic cyst, the walls of which exhibit a great thickness.

The wall is composed of three layers, the outermost of which is the fibrous capsule of the kidney; the median is of connective tissue, in which are vessels and remnants of atrophic glomeruli and uriniferous tubules, with a few elastic fibers; the innermost is of pavement or cuboid epithelium, usually smooth but sometimes containing remains of trabeculae and septums. The wall, however, is subject to considerable variation; sometimes it consists of only two layers without epithelium, or, again, it has several layers of epithelium, in some places even hornified. Calcareous salts may be found within the wall at times.

The content of the cyst is a serous fluid (sometimes serohematic), usually straw or amber colored; it may be clear or turbid or sometimes even gelatinous. Its specific gravity varies from 1.002 to 1.018. Its chemical composition, however, is rather constant; it consists of water, albumin, chlorides, phosphates, sulphates, serum, globulin, fats, cholesterol crystals and urea. The presence of urea has been the subject of some controversy, some authors contending that no element of the urine is ever present. The consensus, however, is that urea is commonly present, though in minute quantities. There are also found epithelial cells, lymphocytes, leukocytes and a few red blood cells.

As the cyst grows, it forms adhesions to the walls of other nearby organs, such as the spleen, the pancreas, the ascending and the transverse colon, the lower surface of the liver, the duodenum and even the stomach. In cases in which it attains a great size, it may also adhere to the abdominal wall at various points, or to the diaphragm if the cyst is located at the upper pole. As a rule it is sessile and in most intimate relation to the renal parenchyma, from which its enucleation is difficult and sometimes impossible. In rare cases, however, a pedicle connecting it with the upper pole or with the hilus is present; in these cases the cyst causes extrarenal pressure on the pelvis of the kidney.

In the typical uncomplicated cyst, there is no communication with the renal pelvis or calices. There are cases, however, in which an opening into a calix develops from infection or other cause (as for example in cases of echinococcic cysts); this at once causes a change in the clinical picture, since now the content of the cyst and the urine within the renal pelvis inevitably mingle, and complications arise. Occasionally a cyst wall thinned to the point of rupture may break through into any neighboring hollow organ against which it has been forcibly pressed in its growth. According to the type of lesion or fluid found in the renal cyst, the latter may belong to any one of the different types of cyst established in the clinicoanatomopathologic classification presented in this paper. Finally, it is not unusual to find reported in the literature hemorrhagic serous cyst associated with renal neoplasm: adenocarcinoma (Scholl), carcinoma (Le Comte), sarcoma (Crabtree), Wilms's tumor (Neff), hemangioma (Begg), hypernephroma (Cun-

ningham), papillary cystadenoma (Colston). Bockenheimer, Moynihan, and Judd and Simon reported cases in which the cyst was associated with horseshoe kidney; Fowler described a case in which there were anomalies of the renal blood vessels. In my own series, there is 1 case of the bifid type of renal pelvis, and another 1 in which the nephrectomized specimen removed at operation revealed the presence of a malignant Wilms tumor attached to the bottom of the renal cyst.

DIAGNOSIS

As recently as 1925, Laquière stated that in only 11 cases had a positive diagnosis of solitary cyst of the kidney been made preoperatively among 121 cases that he had been able to collect from the literature. Since the presence of a cyst is not revealed by any modification of the urine and since the functional capacity of the affected kidney is sometimes actually better than that of the other kidney, the existence of such a cyst has seldom been recognized before operation and the demonstration of it has constituted one of the most difficult problems. In 1932, Simkow brought the number of cases in which preoperative diagnoses were made up to 33 in his total collection of 315 cases.

This failure to recognize the condition has been due to the fact that in the vast majority of cases there is no communication between the cyst and the renal pelvis, and the cyst, being in the cortex, thus remains a thing apart from the urinary system (fig. 2 *A, B* and *C*). The patient will ordinarily first consult a general practitioner for symptoms unrelated to the urinary tract and will be examined for troubles in the gastrointestinal organs; the result of this has been that not a few laparotomies have been performed on the basis of a wrong diagnosis. As a rule the patient does not reach the urologist until the cyst has attained considerable size, causing it to exert pressure on the urinary passages and thus to attract attention to a possible abnormality in this region.

The history and the subjective symptoms of the patient will therefore throw little light on the diagnosis since they are identical with those of other conditions in which there is compression and obstruction in the urinary excretory tract. The patient reaches the urologist only when objective symptoms occur, such as painless hematuria, frequency of urination, dysuria or pyuria. Physical examination may then reveal the presence of an enlarged palpable kidney and sometimes of an elastic tumorous mass on palpation of one or the other side of the abdomen. However, there is so little characteristic about this that it is impossible to say to what organ it belongs or whether it is a cyst or a neoplasm, and if the cyst is in the upper pole of the kidney it may not be palpable at all. The composition of the blood will ordinarily be normal.

Cystoscopy will show nothing characteristic that might not be observed in various diseases of the urinary tract. Catheterization of the ureters may confirm the evidence of obstruction on one side, and in the presence of a palpable mass, usually painless, may direct the diagnosis toward that of tumor but will not reveal whether the mass is within the kidney or is making pressure from outside that organ; nor will it disclose the nature of the tumor mass.

Roentgenography, intravenous urography and retrograde pyelography, then, constitute the principal means of recognizing large serous cyst of the kidney. In the pyelogram, if the cyst is of sufficient size to bulge into the renal pelvis or a calix, a filling defect will be seen producing a deformity of that cavity.

In the great majority of cases the pyelogram will be normal if the cyst is relatively small and does not encroach on the calices or the renal pelvis. If, however, a small cyst is growing close to a calix or the renal pelvis and is so located as to exert pressure, the pyelogram will reveal this fact. This is shown in 3 of my cases hereinafter reported.

When the cyst is at the lower pole, it is so likely to cause hydronephrosis that any slight flattening which the pressure of the cyst itself may make on the pelvis is likely to be masked by the shadow of the hydronephrotic sac. In cases in which the cyst is large enough to displace the ureter, cause obstruction and interfere with drainage, it is likely to betray its presence also when other means of examination are employed.

Compression of the calix that lies nearest to the cyst is highly suggestive of the presence of a solitary renal cyst. One or more calices may be shortened, blunted or in some instances wholly obliterated. As pressure increases with the growth of the cyst, the pyelogram reveals retraction, flattening or elongation of calices that were previously normal. For this reason it is desirable to repeat the making of pyelograms from time to time when the existence of a cyst is suspected. In cases in which the cyst arises not from either pole but on the mesial border of the kidney, the calices remain normal, but the adjacent portion of the pelvis itself becomes flattened under the compressive action of the cyst.

In many cases in which the patient is properly prepared, the outline of the cyst can be clearly made out in a roentgenogram, especially of a cyst in the lower pole. The margin of the cyst will be continuous with the kidney, but a difference will be observable between the density of the cyst and that of the renal organ. The ureter will frequently show displacement at the same time. The cyst is recognizable by its smooth round shadow, which contrasts in contour and density with the shadow of the kidney and the other adjacent organs. Since the fluid within the serous cyst is nearly transparent, the line of the psoas muscle can be readily visualized through it, especially when the cyst is at the lower pole; this would not be possible if the tumor mass were a solid neoplasm.

When the cyst is at the upper pole, the diagnosis is much more difficult and is most frequently impossible. In such cases the weight of the cyst forces the kidney downward, resulting in ectopy of the organ, which may be recognizable in a roentgenogram. Pressure applied on the cystic mass, when this is palpable, was found by Ormond to move the renal pelvis downward to a sufficient extent to show in a pyelogram; a difference was observable between pyelograms made before and after the application of such downward pressure.

According to Quinby and Bright, the diagnosis of cyst at the upper pole of the right kidney has seldom been made preoperatively; this was accomplished in only 5 of 30 reported cases. Such a cyst is easily mistaken for a tumor of the gallbladder or some other pathologic condition in the liver. When a pyelogram is made, it may be possible to diagnose a tumor of the kidney but not to make the differentiation between a neoplasm and a benign cyst in advance of operation. According to these authors, pyelography gives the best information, having shown deformities or displacement of the upper calices in 75 per cent of the 36 cases they analyzed in which the upper pole was the site of the cyst.

Renal arteriography, needle aspiration of the cyst and injection of air into the cyst as a contrast medium, particularly after the fluid of the cyst has been aspirated, are methods of diagnosis which have been used and which may be recommended in certain difficult cases, although in my series the cyst was aspirated in only 1 case for the purpose of diagnosis and treatment, in order to note whether it was refilled a short time afterward, as commonly happens after the aspiration of the fluid in hydrocele of the tunica vaginalis.

In summary, the urographic evidences of a large solitary cyst of the kidney may be as follows: (1) compression of the renal pelvis or of one or more calices; (2) changes in the position of the axis of the kidney; (3) inward displacement of the ureter; (4) displacement or rotation of the renal pelvis upward or downward; (5) visualization of the shadow of the cyst; (6) crescent shape of the renal pelvis or of a calix; (7) calcification of the cyst walls in some cases; (8) visibility of the psoas muscle through the walls of the cyst; (9) shadow of the cyst superimposed on the kidney shadow; (10) visualization of the cyst furnished by pyelovenous backflow.

In a pyelogram solid tumor of the kidney as a rule shows more marked invasion of the calices and the renal pelvis, since the growth of the tumor extends inward to occupy the renal parenchyma, while the cyst tends to spread outward. The pyelogram of the tumor is more disorganized and more bizarre and follows no such rule of uniformity as does that of large simple cyst of the kidney. Further, in cases of

renal cyst the shadow of the kidney itself is usually not enlarged, while a malignant tumor of the kidney causes considerable increase in the size of the shadow.

However, there are cases in which the differential diagnosis of large serous cyst of the kidney is not complete without proper surgical exploration of the cyst, particularly when the patient has a history of hematuria. Such exploration cannot be dispensed with in doubtful cases since to overlook the presence of an associated lesion concealed within the cyst or the kidney, such as malignant tumor, may be more serious and of greater clinical significance for the final prognosis than the apparently benign cyst itself.

Sometimes when the differential diagnosis of cyst of the kidney is doubtful, the repetition of pyelographic studies furnishes a sound criterion. In fact, retrograde pyelograms should be taken with the patient in both the Trendelenburg and the erect position; lateral pyelograms also should be taken whenever indicated, since, as happened in 1 of my cases hereinafter reported, one of the calices may communicate with the renal cyst; when this occurs the pouch or sac of the cyst may be faintly delineated in one of the good films of the pyelogram, and this will serve to clarify the diagnosis.

REPORT OF CASES

CASE 1.—A woman complaining of pain in the right upper quadrant of the abdomen radiating to the right lumbar region of over eight years' duration had twice been operated on elsewhere—first, ten years previously for chronic appendicitis and again eight years later for a cyst in the right ovary, both times without relief. Urographic studies revealed nephroptosis on the right with a kink of the right ureter, for which she refused operation. After several years of palliative treatment, she finally consented to operation for the condition in the right kidney. At operation a moderate-sized renal cyst attached to the upper pole of the right kidney was found. The cyst was resected, nephropexy was accomplished, and a cure was effected.

Mrs. M. J. A., a housewife 32 years of age, was referred on Feb. 8, 1934, complaining of pain in the right upper quadrant of the abdomen radiating to the right lumbar region of ten years' duration. She had also slight frequency of urination with dysuria and nocturia. The patient had been married for ten years but had no children, although her menstrual periods were regular. About ten years previously she had been operated on elsewhere for chronic appendicitis and again two years before my examination for removal of an ovarian cyst, but the persistent pain in the right upper quadrant continued to "nag her off and on" without relief. She had roentgen examinations of the gastrointestinal tract and the gallbladder elsewhere, but no definite diagnosis was made. On physical examination the two scars of previous operations were observed in the lower part of the abdomen. The right kidney was low in position, somewhat enlarged, tender and easily palpable; the left kidney was not palpable. Urinalysis showed the presence of a few pus

and red blood cells, albumin and bacteria. The blood pressure was 100 systolic and 60 diastolic. The patient was ill, thin, nervous and anemic. Cystoscopic examination with catheterization of the ureters and differential renal functional test revealed that both kidneys had good urea excretion and phthalein elimination. Microscopic examination revealed pus cells and blood cells in the specimen catheterized from each kidney. Roentgenograms were taken with catheters and instru-

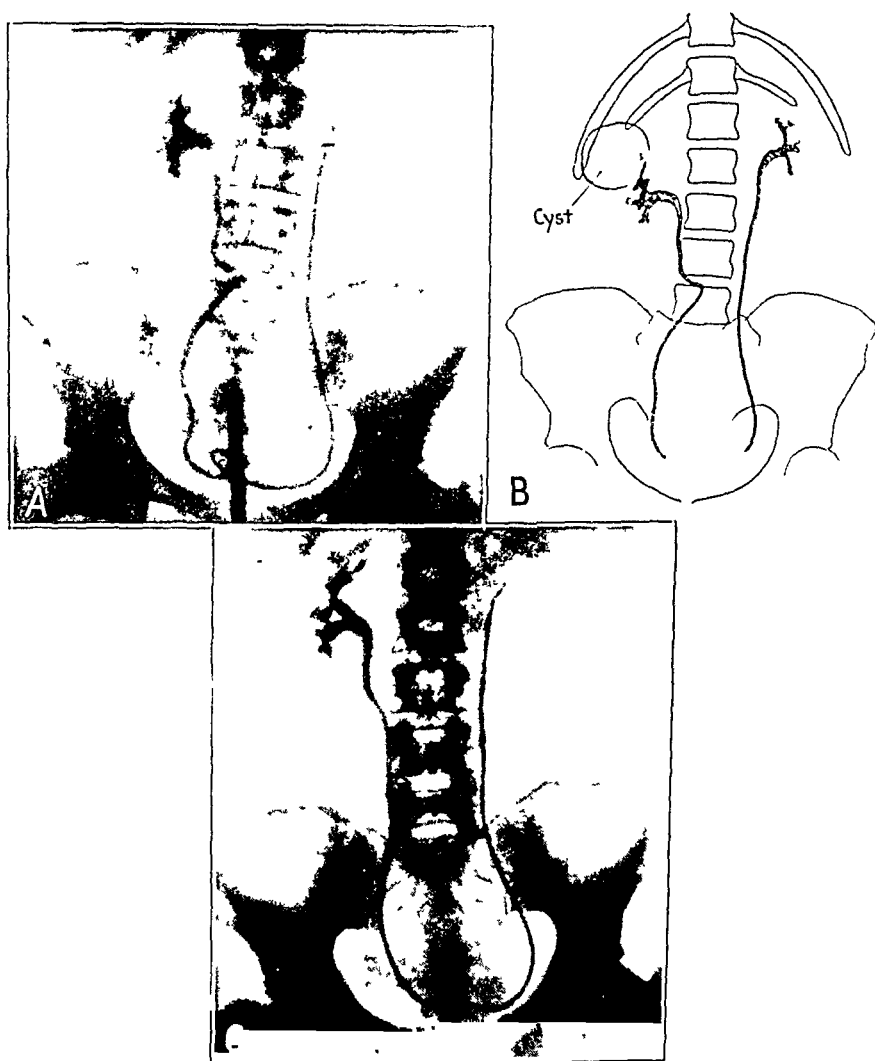


Fig. 2 (case 1).—Pyeloureterograms taken before and after operation; the diagnosis of large serous cyst was made at operation: *A*, right pyeloureterogram showing marked nephroptosis and kink of the ureter; there is a barely visible suggestion of a cyst at the upper pole. *B*, drawing from bilateral pyelogram showing the anatomic position of the cyst found at operation in the upper pole of the right kidney. *C*, right pyeloureterogram one year later. Note the restoration of the right kidney and the ureter to normal position.

ment in position; retrograde pyelograms and pyeloureterograms also were made. These disclosed the presence of nephroptosis on the right, a kink in the right ureter and narrowing of the ureter with evidence of pyelitis and pyelonephritis (fig. 2 *A*).

For this condition the patient received a short course of cystoscopic treatments with dilations of the ureter and lavage of the renal pelvis. She was given a low protein diet, forced to take fluids and treated with urinary antiseptics. After she had been seen by a gynecologist and given treatments for sterility, the patient was again sent to me five years later, on Feb. 2, 1939, complaining of persistent dragging pain in the right upper quadrant and the right lumbar region, definitely localized in the right kidney. Nephropexy was again advised. The patient finally accepted operation and entered the Murray Hill Hospital on Feb. 14, 1939, where an operation on the right kidney was performed. A cyst about the size of an orange was found occupying the upper pole of the kidney and plastered by adhesions to the parietal layers of the peritoneum (fig. 2B). The kidney with the cyst was freely mobilized by nephrolysis and ureterolysis, then the cyst was clamped, the fluid was aspirated, and the sac was resected (fig. 9I). Interrupted sutures were placed at the edge of the cystic sac and that of the proper capsule of the kidney, after which nephropexy was accomplished by fixing the upper pole to the eleventh intercostal space, and the wound was closed in the usual manner, a small cigaret drain being left at its upper angle. The patient had an uneventful convalescence, and the wound healed by primary union. The aspirated fluid was amber in color, and the cyst did not appear to be connected with the upper calix or the renal pelvis. The patient was seen in the office one month later with the wound firmly healed, and she felt happy about the results obtained. One year later she came back at my request for a complete check-up. At that time she was again examined cystoscopically. Renal function from both kidneys was found to be normal. Retrograde pyelograms disclosed that the kidney operated on was in a perfectly normal position and exhibited good drainage as the result of the resection of the renal cyst in the upper pole and the nephropexy (fig. 2C). The patient seemed to have recovered fully, since she stated that she had gained more than 30 pounds (13.6 Kg.), felt comfortable and was free from symptoms.

While the result of the resection of the renal cyst followed by nephropexy has been highly gratifying in this case, it must be admitted that the diagnosis of the cyst was made only at the time of operation, owing to the difficulty of preoperative diagnosis of the early renal cyst.

CASE 2.—A man suffering from hypertension had an attack of painless hematuria of four days' duration, for which he had been examined elsewhere and a diagnosis of tumor in the left kidney made. At the time of my urologic and urographic examination, I diagnosed a solitary cyst at the upper pole of the left kidney; this was confirmed at operation. Partial nephrectomy was planned for removal of the large renal cyst attached to the upper pole of the kidney, but at operation such an enormous cyst was found (it had destroyed more than half the parenchyma and seriously compromised the blood supply of the kidney) that total nephrectomy was carried out with curative results.

Mr. F. R. V., 60 years of age, was referred for examination on July 6, 1939. He had a history of having had an attack of painless hematuria in December 1938 of four days' duration; complete urographic examination had been carried out elsewhere and a diagnosis of tumor of the left kidney made. He gave a history of having received treatment for high blood pressure; at the time of examination the blood pressure was 250 systolic and 150 diastolic. On physical examination, the patient was observed to be well built but decidedly nervous, emaciated and anemic. The abdomen was distended; the kidneys were not palpable. Rectal

examination disclosed slight enlargement of a leathery prostate. The urethra was permeable to sound F. 25. There was about $\frac{1}{2}$ ounce (14.8 cc.) of residual urine in the bladder. On the left there was evidence of a hydrocele of moderate size. The patient stated that roentgen examination of the gastrointestinal tract and the gallbladder had revealed no abnormalities. Urinalysis showed the presence of blood and pus cells with clumps as well as albumin and innumerable bacteria, streptococci and staphylococci, which persisted in many urinary reports. Chemical examination of the blood revealed the nonprotein nitrogen to be 42.86 mg. per hundred cubic centimeters, indicating marked urea retention; creatinine was 2.2 mg. A blood count disclosed secondary anemia. The patient was examined cystoscopically on July 11, 1939, when plain roentgenograms and bilateral retrograde pyelograms were taken. The kidney function was slightly diminished on the left side compared with the

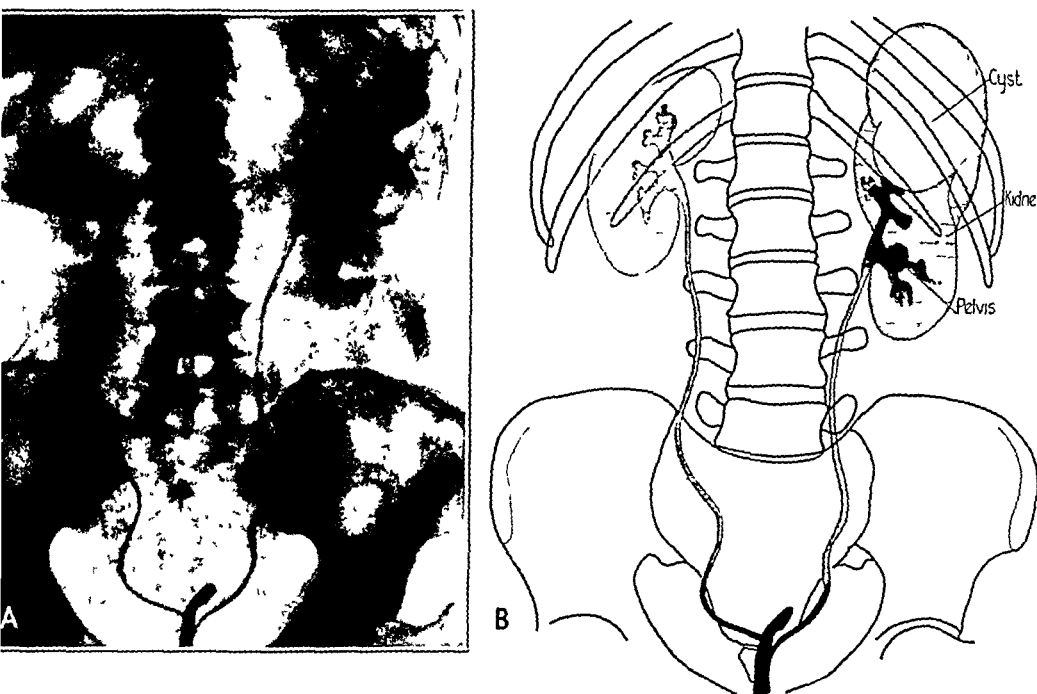


Fig. 3 (case 2).—In this and the following figure are shown various pictures of a large solitary cyst in the left kidney of a man 60 years of age for whom a diagnosis of left renal neoplasm had been made but in whom urographic examination disclosed the presence of a large solitary serous cyst of the left kidney, a diagnosis confirmed at operation. *A*, left pyeloureterogram showing a renal pelvis of the bifid type with definite flattening of the upper calix and a faint outlining of the cyst at the upper pole of the left kidney; revealing also a slight pyelovenous backflow with evidence that the opaque substance has entered the lymphatics surrounding the renal pelvis. *B*, drawing from bilateral pyeloureterograms indicating the actual size and position of the cyst in the upper pole of the left kidney which was diagnosed before operation.

right as to both urea estimation and phthalein elimination. One of the pyelograms disclosed that the opaque substance had spread beyond the upper calix of the left kidney, showing a round shadow which gave the impression of a large solitary

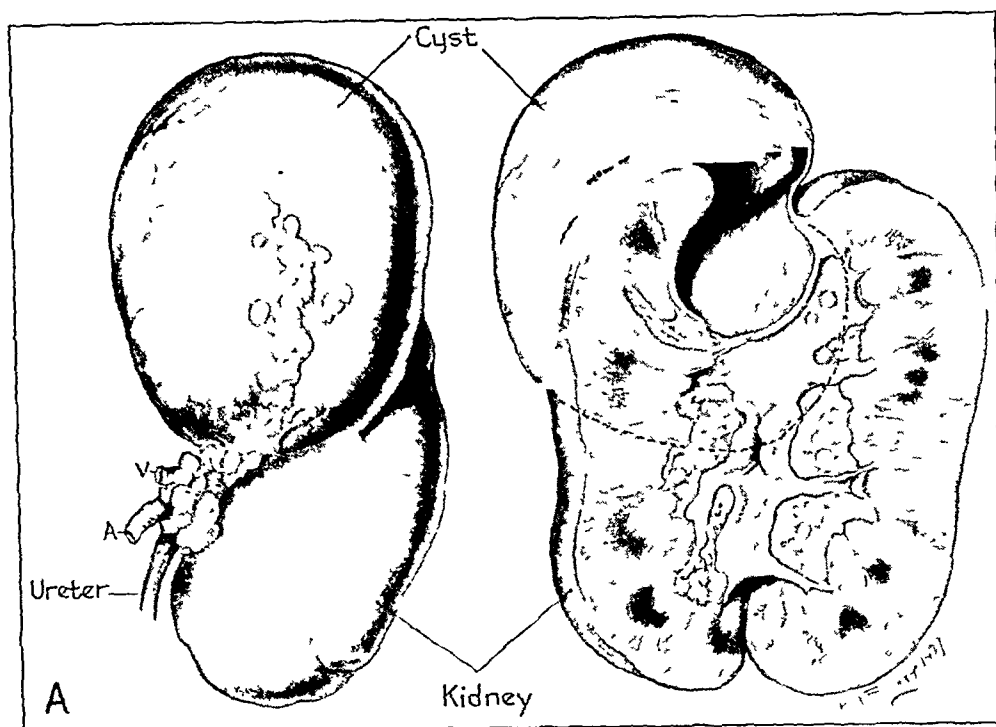


Fig. 4 (case 2).—*A*, drawing of the specimen removed at operation, consisting of the left kidney and the large serous cyst attached to the upper pole. Two views are seen: one showing the appearance before opening; the other revealing the relation of the cyst to the kidney as seen after opening. The cyst extended down the posterior aspect of the kidney almost to the middle of the organ, but had no communication with the renal pelvis. The entire mass of the kidney with its cyst was removed by nephrectomy with gratifying results. *B*, photomicrograph of the histologic section made from the specimen removed at operation showing how the fibrous connective tissue of the cyst wall has encroached on the fairly normal renal parenchyma, which exhibits merely slight atrophy in the kidney substance directly in apposition with the cyst wall, due to the compression exerted by this benign cystic mass.

renal cyst attached to the upper pole (fig. 3*A* and *B*). The left pelvis was bifid in type, and there was a slight degree of pyelovenous backflow. A diagnosis of large solitary cyst of the left kidney with bifid left renal pelvis was made. The patient was admitted to Doctors Hospital on July 13, 1939 and was prepared for operation on the left kidney. He received daily intravenous infusions and three blood transfusions. After two weeks all the tests were repeated and revealed a definite improvement. Nephrectomy on the left was carried out on July 25, 1939 with the patient under anesthesia induced with cyclopropane. The kidney was exposed in the usual manner by incision in the left lumbar region. When the fatty capsule was opened, the large cyst was found attached to the upper pole of the kidney and extending far down on the posterior surface. Resection in order to save the kidney was at first considered, but owing to the anomalous blood supply of the organ and the fact that the line of demarcation of the cyst extended posteriorly down to the renal pelvis and also in view of technical difficulties with the pedicle for the remaining portion of the kidney, it was decided instead to clamp the pedicle and accomplish nephrectomy. A cigaret drain was left in the upper angle of the wound, which was closed in the usual manner. Convalescence was uneventful. The patient left the hospital on Aug. 14, 1939 with the wound almost closed except for a small sinus in the upper angle, which after several dressings and proper care finally healed. He had gained in weight, and his general health was considerably improved. There was a drop in blood pressure to 160 systolic and 90 diastolic after nephrectomy.

Histologic examination of the specimen removed at operation was made by Dr. H. R. Muller at Doctor's Hospital and disclosed the following information: The kidney was slightly enlarged owing to the presence in the upper pole of a cyst 8 or 9 cm. in diameter. This cyst had a thin fibrous wall and replaced a large portion of kidney substance. It contained clear liquid. It was close to the upper portion of the pelvis but did not actually communicate with the pelvis (fig. 4*A*). The pelvis had two parts, draining respectively the upper and the lower pole, but these united and had a common ureteral outlet. The cortex and the medulla had normal markings, and the capsule stripped off easily, leaving a smooth surface. The wall of the cyst was composed of fibrous connective tissue in which there were foci of round cell inflammation. It became fused and was continuous with the capsule of the kidney where they met. Glomeruli, tubules of both the cortex and the medulla and blood vessels became involved in the capsule and showed atrophy in the narrow zone of kidney substance directly in apposition with the cyst wall (fig. 4*B*). These structures being gradually drawn into the wall of the capsule showed progressive enlargement and encroachment on the kidney substance.

Pathologic Diagnosis.—The patient had a benign cyst of the kidney with chronic productive and exudative inflammation in the wall. There were atrophy of the adjacent kidney substance and a double pelvis of the kidney.

This case serves to illustrate the favorable and definitely good prognosis that exists when one is dealing with what proves to be a large solitary cyst of the kidney and not a renal neoplasm. It also shows that notwithstanding the advantage of achieving a urographic diagnosis previous to operation, the urologist must choose at operation the type of procedure that then proves most suitable for the individual patient. It also serves to emphasize that while a conservative procedure of

resecting the cyst may save a properly functioning kidney, it is wiser, when an anomalous blood supply is found in the pedicle and the kidney cannot be saved, to carry out nephrectomy in order to obtain permanent cure.

CASE 3.—A young woman had suffered from persistent pain in the right lumbar region since the age of 12; ten years later the pain became aggravated. She lost weight and suffered from gastrointestinal disorders. Urographic examination disclosed marked nephroptosis on the right with inward rotation and compression of the lower calix and the renal pelvis. At the time of operation, a cyst of moderate size was found attached to the lower pole of the right kidney. In view of the fact that compression by the cyst had destroyed a great part of the renal parenchyma and also because of the anomalous blood supply of the kidney, nephrectomy was carried out with gratifying results.

Miss J. M. A., 24 years of age, was examined on Aug. 20, 1940 by Dr. J. P. Lopez of Habana, Cuba, through whose courtesy I am reporting this case in detail. She complained chiefly of pain in the right lumbar region radiating to the bladder region, of several years' duration. She was thin and anemic and suffered from gastrointestinal disorders and slight frequency of urination, dysuria, microscopic pyuria and hematuria. On physical examination, the right kidney was palpable, tender and low in position. A round mass about the size of an orange could be felt attached to the lower pole of the kidney. The left kidney was not palpable. The patient had been examined on several previous occasions and the diagnosis of floating kidney made. Cystoscopy disclosed normal ureteral orifices and a normal bladder. Both ureters were catheterized. The specimen collected from the right kidney was hazy and contained 19 per cent pus cells per microscopic field and *Bacillus coli*; the urea content was 8 Gm. per liter. The specimen from the left kidney had only 2 or 3 pus cells and 13 Gm. of urea per liter. Indigo carmine appeared in fifteen minutes from the right kidney and in five minutes from the left. A phenolsulfonphthalein test done at another sitting disclosed 22 per cent elimination from the right kidney and 34 per cent from the left; this showed that the function of the right kidney was diminished. A roentgenogram and plain films taken with catheters and instrument in position revealed that the right ureteral catheter was deviated toward the spinal column. Retrograde pyelograms disclosed evidence of slight hydronephrosis with some inward rotation of the entire pelvis. The two lower calices were compressed, and there was also a marked degree of nephroptosis (fig. 5). The left pyeloureterogram was entirely normal. The blood composition, blood count and blood pressure were almost within normal limits. After a diagnosis of right nephroptosis and possible tumor or cyst of the lower pole of the right kidney, operation was performed with the patient under general anesthesia. The kidney was exposed in the usual manner by incision in the lumbar region. A large serous cyst attached to the lower pole was readily seen. It was so deeply situated within the renal parenchyma that almost half of the organ was destroyed by the pressure. Since the kidney could not be saved owing to the anomalous blood supply in the pedicle and evidence of atrophy and diminished function, the pedicle was clamped and nephrectomy carried out in the usual manner. The results obtained were excellent. The specimen removed at operation showed a certain degree of atrophy of the renal parenchyma and the presence of pyelonephritis; it also could be seen that the sac of the cyst had not communicated with the lower calices, to which the cyst was firmly attached.

This case illustrates that when rotation downward and inward with compression of calices and the adjoining pelvis is demonstrated, a diagnosis of large solitary serous cyst of the kidney is warranted in most instances. If the diagnosis had been made early enough, it is possible that heminephrectomy or simple resection of the cyst followed by nephropexy might have saved the organ. However, nephrectomy was



Fig. 5 (case 3).—Bilateral pyeloureterogram showing a large solitary serous cyst of the lower pole of the right kidney in a woman with marked nephroptosis. The cystic condition was diagnosed at the time of operation. The picture discloses a normal kidney on the left side and marked nephroptosis on the right with downward and inward rotation of the major and the minor calices and inward compression of the right ureter by a faint rounded mass in the lower pole of the right kidney (indicated by arrows) which shows evidence also of pyelitis and pyelonephritis. At the time of planned right nephropexy a large solitary cyst of the lower part of the right kidney was disclosed; in view of the fact of an anomalous blood supply, nephrectomy was carried out and resulted in cure.

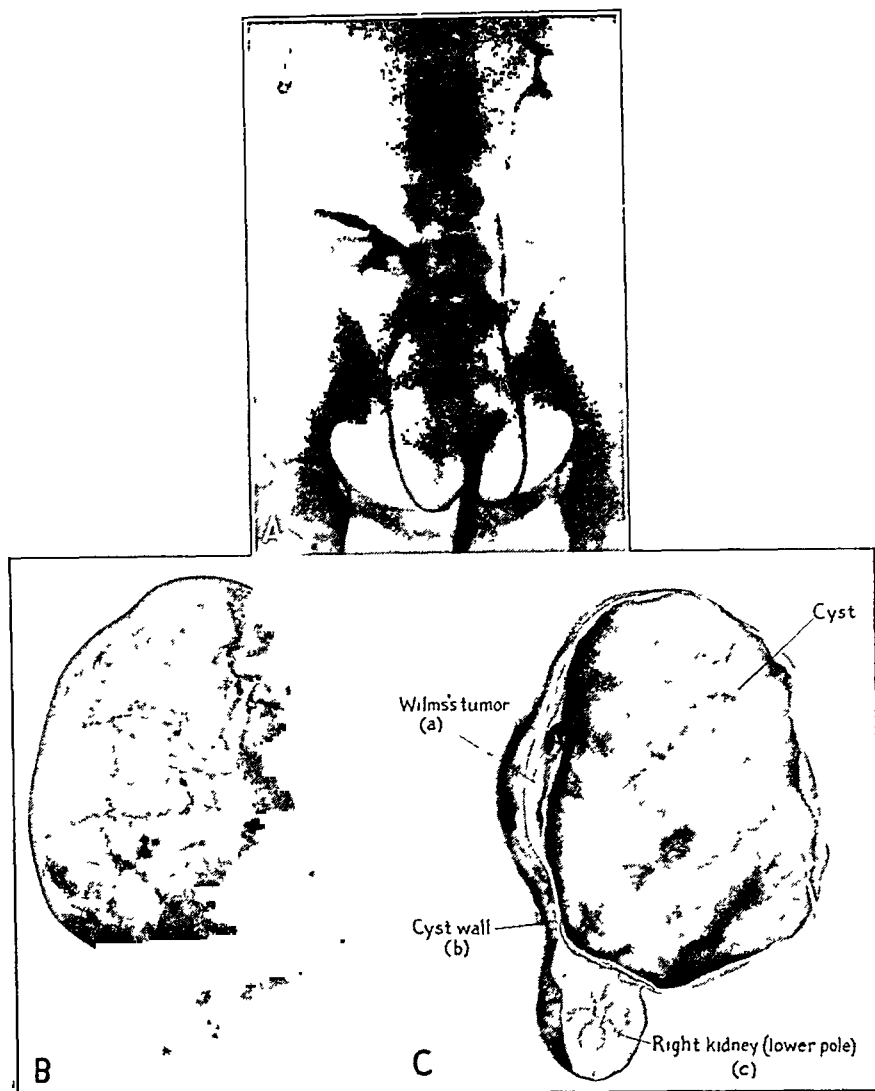


Fig. 6 (case 4).—A gigantic solitary renal cyst in a girl 18 years of age contained 5 liters of fluid and also within its walls Wilms's tumor. The cystic condition was diagnosed urographically and was confirmed at operation. *A*, bilateral pyeloureterograms revealing a normal kidney on the left side and congenital ectopy on the right with definite flattening of the upper calix, slight inward rotation of the renal plexis and displacement of the right ureter, strongly suggesting the presence of a large solitary cyst of the upper pole of the right kidney. *B*, drawing of the specimen removed at operation by transperitoneal nephrectomy, representing the enormous solitary cyst of the upper pole of the right kidney which completely destroyed the upper half of the organ. *C*, interior view of the gigantic cystic sac showing the smooth surface of the capsule of the cyst attached to the upper pole of the right kidney and revealing the association of a malignant growth with the benign cyst.

justified by the advanced destruction of the renal parenchyma, as the only means of obtaining permanent cure.

CASE 4.—*A gigantic solitary renal cyst with Wilms's tumor in a young girl was diagnosed urographically. Transperitoneal nephrectomy was performed, and*

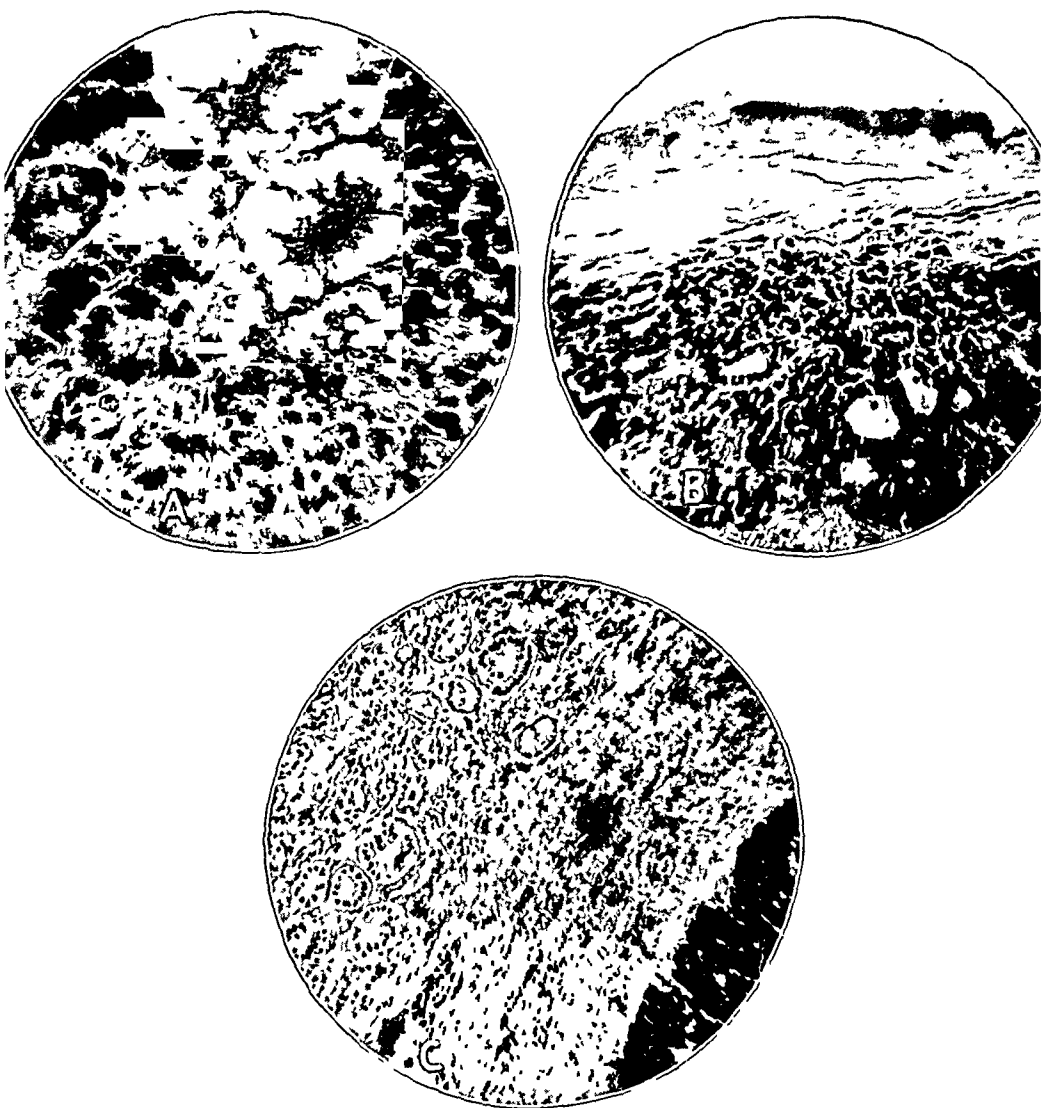


Fig. 7 (case 4).—Photomicrographs of the histologic sections of the cyst and the kidney revealing: *A*, the typical structure of Wilms's tumor arising from the walls of the capsule of the cyst; *B*, Wilms's tumor and cyst wall; *C*, renal tissue, hyalinized capsule and tumor.

at the time of operation the specimen proved to be a large solitary cyst containing 5 liters of chocolate brown fluid. Attached to the base of the walls of the cyst was a malignant growth.

Miss M. S., 18 years old, was examined by Dr. E. J. Daly of Jersey City, N. J., who gave me permission to report the case. The patient's chief com-

plaint was moderate pain on the right side of the abdomen, not radiating to the right lower quadrant, associated with nausea of three weeks' duration. On physical examination there was a large cystic mass which was not tender and which filled the entire abdomen. The left kidney was not palpable. The patient underwent exploratory laparotomy on Feb. 6, 1936, when appendectomy was performed, with removal in addition of a small ovarian cyst. On April 4, 1937, she was readmitted after having suffered a fall flat on the abdomen, after which the persistent pain became more severe and was again accompanied by nausea and vomiting. The clinical and the laboratory findings were noncontributory. Roentgenograms of the chest and the gallbladder and a series of gastrointestinal roentgenograms, including some in making which enemas of barium sulfate were used to obtain visualization, also failed to reveal any abnormalities except deviation of the transverse colon, which looked as if it was pushed downward by an abdominal tumor mass. At this time the patient received a complete urologic and urographic examination. Intravenous urograms disclosed that the pelvis of the right kidney was displaced downward and was low in position. Cystoscopy and retrograde pyelography revealed a congenital ectopic kidney on the right side situated almost at the level of the sacrum and the crest of the ilium; the pelvis was rotated downward and inward. A lateral pyelogram also disclosed flattening of the upper calix; this suggested a filling defect produced by compression of the cyst or the tumor attached to the right kidney (fig. 6A). Another exploratory laparotomy was performed, during the course of which transperitoneal nephrectomy was carried out successfully; the right kidney was removed with an enormous cyst the size of the head of a fetus attached to its upper pole (fig. 6B). The specimen removed at operation contained 5 liters of chocolate brown fluid. Examination of the cystic fluid revealed the presence of many red blood cells and occasional white blood cells. There was no evidence of urea; this proves that while the cyst arose from the renal parenchyma, it in no way communicated with the upper calices or the renal pelvis. When the cystic cavity was opened, a flat infiltrating tumor was found attached to the wall of that part of the cyst which was adherent to the renal parenchyma (fig. 6C). Histologic examination revealed that this was Wilms's tumor (fig. 7).

This case illustrates the association of a malignant growth with a large solitary cyst of the kidney; such a possible association must always be kept in mind in treating younger persons. Nephrectomy in these cases is the procedure of choice for removal of the malignant tumor.

CASE 5.—A bilocular left renal cyst was diagnosed urographically.

Mrs. H. A. R., a housewife aged 66, consulted me on Sept. 18, 1939, about her complaints of shortness of breath, high blood pressure, severe pain in the precordial region and difficult respiration. She had been receiving treatments for obesity and for the cardiac and aortic condition for several years. She complained also of frequency of urination day and night, chronic constipation and slight pain and dulness in the left side of the abdomen radiating to the left lumbar region. On physical examination the right kidney was slightly palpable; the left kidney was low in position and easily palpated. Apparently, the left kidney was larger and lower down than the right. Urinalysis disclosed the presence of an alkaline reaction, traces of albumin, few hyaline casts and leukocytes with clumps; an occasional red blood cell and many bacteria also were present.

In view of these urologic findings a complete urographic examination was recommended. Roentgenograms and intravenous urograms, taken at Doctors Hospital on Oct. 4, 1939, revealed that the right kidney was normal in size, shape and position. The left kidney was lower in position than the right. In a fifteen minute film the pelvis appeared to be bifid in type. There was an overshadow in the outer border suggesting the presence of a large solitary cyst about the size of an orange. There was another round shadow which seemed to push the ureter inward, indicating the presence of another cyst in the lower pole of the same kidney. Although the diagnosis was evident from the intravenous urograms, retrograde pyelograms were recommended to confirm it. However, as the patient's general symptoms had improved with medical care, she left town without further examination.

From the urographic point of view, the diagnosis was definitely that of bilocular large solitary cyst of the kidney. Since, however, the diagnosis was not confirmed by retrograde pyelograms or proved at operation, this case is reported only to illustrate the possibility of urographic diagnosis.

CASE 6.—A solitary cyst of the lower pole of the left kidney was diagnosed urographically.

S. F., a man 41 years of age, consulted me on May 10, 1933, about indefinite pain in his abdomen. He also complained of frequency of urination day and night, dysuria, nervousness, dyspepsia and chronic constipation. Twenty years previously he had an attack of similar pain, for which appendectomy had been done. He stated that he had nevertheless been suffering from these symptoms off and on during all that period. The urine was clear, but microscopically it contained a few pus cells and red blood cells. The prostate was found to be normal by rectal palpation. The right kidney was not palpable; the lower pole of the left kidney was barely made out. The external genitals were normal. Roentgenograms and intravenous urograms revealed an anomaly of the twelfth rib on the left side, in that this rib was much shorter than the corresponding rib on the right side. Intravenous urograms revealed the presence of a small cyst about the size of a tangerine at the level of the lower pole of the left kidney which was deviating the course of the ureter inward. There was also slight compression of the lower calix, which appeared crescent shaped. The urographic diagnosis was that of large solitary cyst of the lower pole of the left kidney.

Retrograde pyelography was recommended but was not carried out. The diagnosis of large solitary cyst was therefore not confirmed or proved at operation. The patient's symptoms subsided under proper medical care, and he left town without a complete urologic check-up.

CASE 7.—A large solitary cyst of the upper pole of the left kidney was diagnosed urographically and treated by puncture and aspiration of the fluid.

J. O., a young man 19 years of age, consulted Dr. J. W. Draper, who permits me to report this case, on Jan. 29, 1938. The patient's chief complaint was urethral discharge. The past history was irrelevant except that he had at times had difficulty in voiding. On physical examination hypospadias with the meatal opening about 1 cm. back from the tip of the glans penis was noted. A smear taken from the hypospadiac meatus was positive for gonococci. The discharge responded to local instillation and sulfanilamide therapy. However, there remained some

shreds in the urine and pus cells in the prostatic secretion. At the end of four months the patient was taken to New York Hospital for a complete check-up. During the course of this examination intravenous urograms disclosed a crescent-shaped defect in the pelvis and the upper calices of the left kidney; this suggested the presence of a renal cyst of moderate size (fig. 8 *A* and *B*). At that time needle aspiration was done and 120 cc. of clear straw-colored fluid removed from the renal cyst. The examination of the fluid for urea yielded negative results. Aspiration of the cyst was not continued because the patient fainted during the procedure. It was not until a year later that another roentgenogram was taken and the cyst again aspirated. Urograms showed the same crescent-shaped filling defect compressing the upper calices and the renal pelvis; they gave the impression of a large serous cyst of the kidney about the size of a grapefruit. At this time the cyst was punctured, and 750 cc. of clear fluid was aspirated. After this

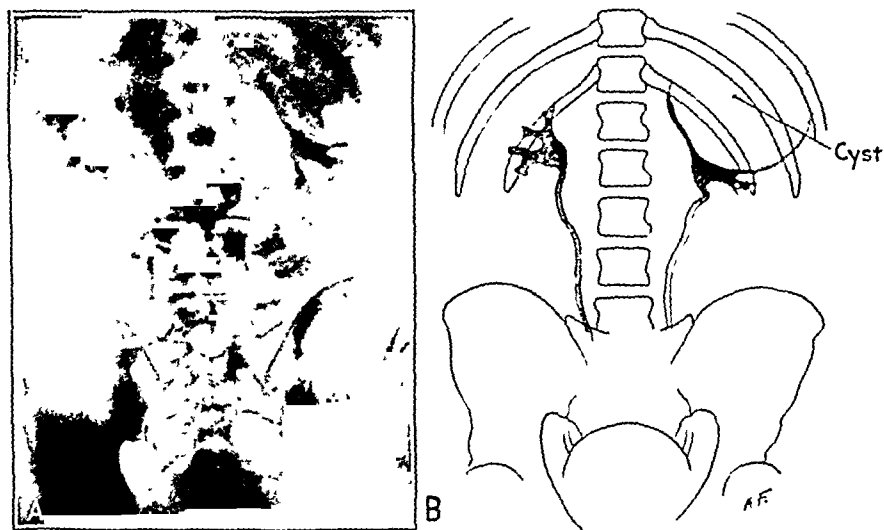


Fig. 8 (case 7).—A large serous cyst of the upper pole of left kidney in a boy 19 years of age was diagnosed by intravenous urography and confirmed by puncture and aspiration of the cyst. *A*, intravenous urogram disclosing a normally functioning kidney on the right and a crescent-shaped compression and elongation of the upper calix on the left side, suggesting the diagnosis of a large solitary renal cyst; this was confirmed by aspiration of 750 cc of fluid, although no operative confirmation was available. *B*, drawing to indicate the anatomic position and the topographic relations of the cyst.

last aspiration the patient left town, and nothing is known regarding his present condition.

Intravenous urograms led to a diagnosis of large solitary cyst of the kidney. Needle aspiration of the fluid confirmed the diagnosis, since it was obvious that the fluid had been drawn from a large serous cyst of the kidney, although no operation was carried out in this case.

CASE 8.—A large solitary cyst of the lower pole of the left kidney was diagnosed urographically.

G. M. M., a man 62 years of age, consulted me on Jan. 3, 1934, about his complaint of left renal colic. He gave a history of having had hematuria and renal

colic twenty years previously, when he passed a small urinary calculus and of having had the same condition again three years before consulting me. During the last twenty years he suffered with a mild pain, which at times became severe, in the area of the left kidney region. On physical examination the abdomen was distended. The right kidney was not palpable. The left kidney was enlarged, readily palpated and tender on pressure. A soft round mass about the size of a large grapefruit could be definitely made out on palpation and apparently was attached to the lower pole of the left kidney. The prostate was enlarged and boggy in consistency. Urinalysis revealed the presence of microscopic pyuria, a few red blood cells, albumin, bacteria and hyaline casts. There was no shadow indicative of stone anywhere in the urinary tract except a certain amount of calcification surrounding the large shadow in the area of the left kidney; this appeared to be a calcification in the capsule of a cyst in that organ. Intravenous urograms disclosed destruction of the left renal pelvis and the lower calices where a crescent-shaped shadow gave the impression that a large solitary cyst was attached to the lower pole of the left kidney. There was also considerable deviation of the left ureter toward the midline, which was in contact with the vertebral column. The patient left town after the diagnosis of cyst of the left kidney. He returned on Nov. 6, 1937, when another intravenous urogram was taken. This examination disclosed the same large round cystic mass causing a filling defect of the left renal pelvis and the lower calices and thus sustained the diagnosis of large solitary cyst of the left kidney made on previous examination.

Urographic studies as well as clinical observation clearly disclosed the presence of a large solitary cyst in the lower pole of the left kidney. Since, however, the patient had no further symptoms relating to the kidney ailment, he did not return for further treatment.

CASE 9.—A large solitary cyst in the lower pole of the right kidney with a double renal pelvis was diagnosed by retrograde pyelograms.

Mrs. C. R., a housewife 55 years of age, was referred to me for examination on Nov. 18, 1935, complaining of pain in the right lumbar region of two months' duration with frequency of urination day and night. She gave a history of having had pyuria, pyelitis and cystitis in 1930 and again in 1932. For several intermittent attacks of pain she had roentgen examination of the gallbladder and the gastrointestinal tract elsewhere. Urinalysis showed evidence of microscopic pyuria and hematuria and a trace of albumin. On physical examination the right kidney was low in position, readily palpable and tender on pressure. The left kidney was not palpable. On Nov. 20, 1935, she was examined cystoscopically; at that time a diagnosis of stricture of the urethral meatus and polyposis of the bladder neck was made. Retrograde pyelograms disclosed right nephroptosis with a renal pelvis of the bifid type and some compression of the lower calices by a rounded superimposed shadow about the size of an orange which suggested the presence of a large solitary cyst in the lower pole of the right kidney. A pyelogram showed the left kidney was normal.

This patient was treated medically and urologically for the condition of the urethral meatus and bladder neck, but since she refused the suggested kidney operation and left town, the diagnosis of large solitary cyst of the right kidney could not be confirmed surgically.

CASE 10.—*A large solitary cyst in the lower pole of the right kidney was diagnosed by pyeloureterograms.*

Mr. E. F., 74 years of age, was referred to me for examination on March 10, 1937, complaining of pain in the right lumbar region of two weeks' duration. The pain radiated to the front and down along the line of the ureter. He had frequency of urination day and night. The voided specimen of urine was clear with a few shreds. Urinalysis disclosed the presence of pus cells and red blood cells as well as traces of albumin. On physical examination the abdomen was distended. The right kidney was low in position, easily palpable and tender on pressure; the left kidney was not palpable. The prostate gland was found by rectal examination to be slightly enlarged and leathery in consistency. There was about 1 ounce (29.5 cc.) of residual urine. The urethra was permeable to sound F. 22. On March 17, 1937, the patient was examined cystoscopically, both ureters were catheterized, and roentgenograms were taken with catheters and instrument in position. Both kidneys had good eliminatory function with regard to urea estimation and phthalein elimination. Pyelography disclosed a crescent-shaped defect, with flattening of the pelvis and downward rotation, and absence of the calices and a round shadow covering the lower pole of the right kidney. The right ureter was also displaced slightly inward, and the position of the kidney was lower than that of the left kidney, which was normal. The pyelocalicial defect produced by compression and the good-sized circumference suggested the presence of a large solitary cyst of the right kidney. A pyelogram of the left kidney showed that it was bifid in type but otherwise normal.

While the pyelographic diagnosis of large solitary cyst of the lower pole of the right kidney was definitely made, it was not confirmed by operation, since the patient was relieved by medical care and since in view of his advanced age and lack of urinary symptoms no operation was advised.

TREATMENT

In regard to the treatment of large serous cyst of the kidney, three different methods must be considered: (1) medical treatment followed by close urologic and urographic observation; (2) treatment by aspiration or injection, which is always to be condemned as fallacious; (3) surgical treatment, which may be either conservative or radical.

Medical Treatment.—In the medical treatment, there must be considered those uncomplicated cases in which the cyst has been an accidental roentgen finding, is asymptomatic, is still of rather small size, has not displaced the organ or caused any compression of the calices, the renal pelvis or the ureter and has not interfered with the function and the normal drainage of these organs; those cases in which there is no evidence of associated disease in the kidney and in which urinalysis or microscopic examination of the catheterized specimen reveals no pus, blood or micro-organisms; those cases in which urographic examination shows that there is no connection of the cyst with the excretory apparatus of the kidney, and finally, those cases in which repeated pyelographic studies show conditions that are within normal limits.

In early cases the asymptomatic cyst may not require any open or surgical treatment but only proper clinical observation from time to time in order that the physician may be assured that the cystic sac is not undergoing a silent rapid growth or causing any further pathologic change. As a rule, urographic studies repeated from time to time will serve to disclose accurately enough the progress of a harmless lesion, and if there is any doubt, the kidney and cyst should be exposed by operation for proper treatment.

Treatment by Aspiration or Injection.—In the so-called nonsurgical treatment of large serous cyst of the kidney, many authors of pre-urographic days advocated puncture with aspiration and injection of the cyst as a panacea. However, this method of treatment, as commonly carried out in the past, has often resulted in serious complications and even death, as one can see from the literature. Thus Lejars reported 4 deaths among 7 patients treated by the method of needle aspiration and injection. Of the 3 patients who survived, none was completely cured of his ailment. In 1906, Simon reported his own use of puncture in the treatment of 5 patients; 4 died, and only 1 survived. Thompson also reported a death following the repeated tapping of an enormous solitary cyst of the kidney.

These considerations led Albarran, Péan, Tuffier and other surgeons of that epoch to give up this unsound and uncertain method of treatment. This so-called harmless procedure should in no way be compared with the simple method of injection and aspiration treatment of hydrocele of the tunica vaginalis, since the kidney is anatomically a deep thoraco-abdominal organ in which the long needle cannot safely be allowed to penetrate in the dark of a closed surgical wound, where it may produce complications and even death through profuse bleeding, formation of renal hematoma and development of peritonitis. The physician may have the sad experience that the sac refills again and that the procedure must be repeated with great inconvenience and discomfort to the patient. It is evident today that this form of treatment is only palliative and not in any sense curative; further, the aspirated fluid can in no way reveal associated disease that may be present, such as a possible malignant growth. Although the method may have its diagnostic possibilities, it should not be considered a routine mode of treatment except in unusual circumstances.

Surgical Treatment.—In the surgical treatment of large solitary serous cyst of the kidney consideration must be given to the type of lesion that may be present in the cyst and the kidney and also to the functional capacity of the organ. Two essential groups of cases are found: (1) those in which a conservative operation can be performed

to save the kidney and (2) those in which a radical operation is indicated for the removal of the kidney and the cyst.

So much progress has been achieved in modern surgical urology since the introduction of pyelography that it is now possible to make an accurate preoperative diagnosis of large solitary cyst of the kidney in most instances. It is therefore obvious that with this type of benign and localized lesion of the kidney the ideal procedure is a conservative operation designed to save as much of the renal parenchyma as possible by simple total removal of the renal cyst.

Conservative Operations: In the group of cases in which conservative treatment is possible, three main types of operation are indicated (fig. 9).

1. When the solitary serous cyst is located in the upper pole, is rather small and not connected with the upper calix, as in case 1 of the series here reported, the kidney and the cyst are surgically exposed by the usual incision in the lumbar region; this is followed by complete nephrolysis and ureterolysis. The cyst is then clamped and aspirated under full vision and resected by scissors from its line of attachment to the upper pole of the kidney. The capsule of the kidney in contact with the surface of the base of the cyst (which has already been removed) is sutured around the kidney by interrupted sutures, and nephropexy is carried out, the upper pole of the kidney being fixed to the eleventh intercostal space in order that the kidney may be brought high up into its normal anatomic position (fig. 9 I). It is worthy of note that in case 1 retrograde pyelograms taken one year after this conservative operation disclosed that the renal pelvis and the calices had entirely recovered their normal form and that the kidney had regained its normal position and function.

2. The second type of conservative operation is particularly suitable for use in those cases in which the benign large solitary serous cyst is situated in the external border of the middle portion of the renal parenchyma; also for use in an occasional case in which the cyst is connected with or so closely attached to one of the calices of the renal pelvis that at the time of operation the calix has to be clamped and tied by transfixed sutures to prevent leakage of urine. The technic of the operation consists in partial renal decapsulation, incising the kidney capsule all around the cyst, finding the line of cleavage and then enucleating the cyst from its renal bed; after this the base of the kidney is clamped and sutured to prevent bleeding or leakage of urine (fig. 9 II). Once the cyst has been removed, the two halves of the renal parenchyma are approximated by interrupted sutures, and a transplanted piece of fat or muscle is placed in the center of the wound to prevent hemorrhage or leakage.

3. When the large solitary serous cyst is found in the lower pole of the kidney and has by its compression destroyed a considerable amount of renal parenchyma, and there is no line of demarcation, it is necessary

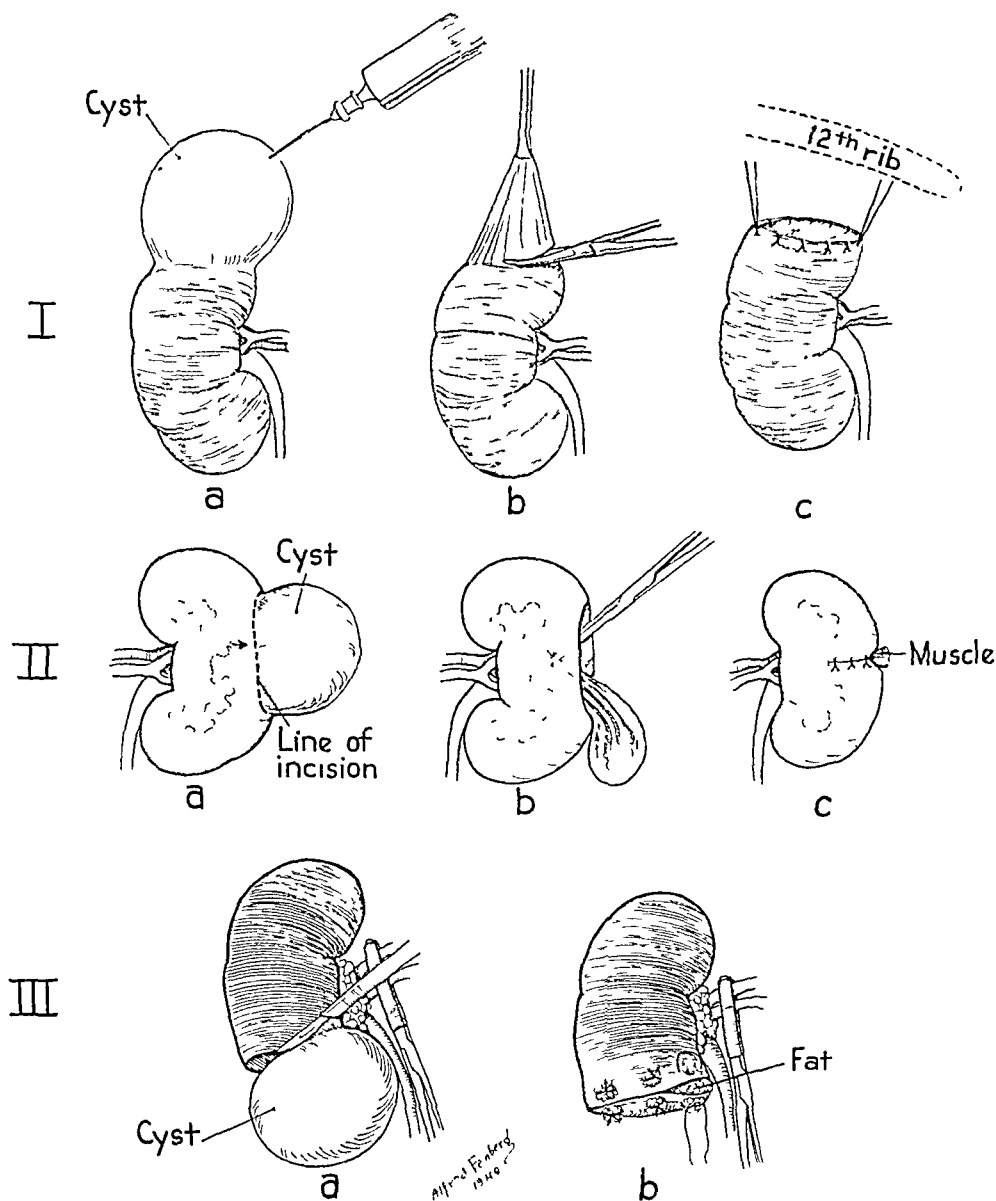


Figure 9

(See legend on opposite page)

to carry out polar amputation, cuneiform resection, heminephrectomy or partial nephrectomy for the removal of the cyst (fig. 9 III). In this type of operation, it is essential to clamp the pedicle with a rubber-shod clamp to prevent hemorrhage from the kidney before performing partial

nephrectomy for removal of the closely adherent cyst. The cut surface of the kidney is then covered with a piece of fat to prevent bleeding, and mattress sutures are placed.

4. Marsupialization of the cyst was recommended by a number of authors in the preurographic era, when the differential diagnosis and the type of cyst could not be established preoperatively. Although this conservative surgical procedure of marsupializing as much of the cyst as possible has its indications in difficult cases, e. g., when the cyst cannot be surgically exposed at the time of operation, and is also useful when combined with nephrostomy in complicated cases in which there is evidence of infection with hydronephrosis or pyonephrosis, it has the

TABLE 2.—*Analysis and Results of Surgical and Nonsurgical Treatment in Ten Cases of Large Solitary Cyst of the Kidney**

Type of Treatment	Patients Cured	Patients Improved	Patients Not Followed Up	Total Number of Patients
Resection of cyst from upper pole of right kidney with nephropexy....	1	1
Lumbar nephrectomy	2	2
Transperitoneal nephrectomy	1	1
Puncture with aspiration of cyst....	..	1	..	1
Cystoscopic treatment with dilation of ureters and lavage of kidney pelvis	2	..	2
Medical treatment	3	3
Total.....	4	3	3	10

* Summary: Of 4 patients operated on, all are cured; of 6 patients not operated on, 3 were improved and 3 not followed up.

EXPLANATION OF FIGURE 9

Operative technic for excision of a large solitary cyst of the kidney:

I. The kidney and the cyst of the upper pole are exposed by a lumbar incision. (a) The cyst is aspirated under vision. (b) The cyst is clamped and resected. (c) Interrupted sutures are placed all around the kidney between the base of the cyst and the fibrous capsule of the kidney; this is followed by nephropexy for suspension of the organ. This procedure was successfully carried out in case 1 (see text).

II. The cyst is located on the external border of the kidney and is close to a calix. (a) The fibrous capsule of the kidney is incised all around the cyst; this is followed by partial decapsulation to gain the line of cleavage of the cyst in its renal bed. (b) The cyst has been emptied as in I; its base close to a calix is clamped, and the calix is sutured to prevent leakage of urine or bleeding. (c) The cyst having been removed, a piece of muscle is interposed between the cut surfaces, and the kidney is sutured as in ordinary nephrotomy.

III. The large cyst at the lower pole has destroyed a considerable amount of parenchyma by compression. (a) The pedicle of the kidney is clamped with a rubber-shod clamp, and partial nephrectomy is accomplished to remove the closely adherent cyst. (b) The raw surface of the kidney is covered with fat to prevent bleeding, and mattress sutures are placed (see text).

disadvantage, nevertheless, of being followed by a lumbar fistula of long standing, which usually requires secondary nephrectomy to obtain permanent cure. Hence it seems best whenever possible to perform one of the three conservative operations already described.

Radical Operations: In the radical surgical treatment of large solitary serous cyst of the kidney, two types of nephrectomy are indicated: the usual extraperitoneal lumbar nephrectomy and the transperitoneal nephrectomy. The latter is more suitable for voluminous cysts that resemble renal neoplasms, as in 1 of the cases reported in this paper. Nephrectomy should be carried out (1) when the kidney is devoid of function, (2) when the cyst has destroyed more than one half or one third of the organ by compression, (3) when there is a short renal pedicle or there are insufficient blood vessels to supply the remaining portion of the organ, (4) when there are obvious technical obstacles to the performance of a conservative operation and (5) when there is evidence of concomitant lesions in the kidney suggestive of a renal neoplasm. Under any of these conditions nephrectomy should be performed, provided that the kidney of the opposite side is functionally and pyelographically normal.

SUMMARY AND CONCLUSIONS

Large solitary cyst of the kidney was formerly regarded as rare, but since the adoption of the systematic use of urography it is known to be of not infrequent occurrence. The condition can now be diagnosed pre-operatively in most instances and should be differentiated from other types of cyst and from associated borderline lesions of the kidney. A clinicoanatomopathologic classification of cystic conditions that may be found in the kidney or in the region of the kidney is presented in table 1. This table serves to emphasize the different types of large solitary cyst of the kidney according to number, size and anatomic location, and especially according to type of lesion and nature of content. It also serves to differentiate three main groups, demonstrable urographically and anatomopathologically, according as the cyst is connected or is not connected with a calix or the renal pelvis or lies in fact altogether outside the kidney structure but within the anatomotopographic region.

The pathogenesis of the large solitary cyst is uncertain, although it is clear that the condition may be either congenital or acquired.

This study with the report of 10 cases has revealed that the symptoms are various and insidious. The condition may be diagnosed urographically, even for patients who have no urinary symptoms or only mild ones, whenever the cyst by compression has produced marked painful symptoms or physical signs of a tumor mass palpable in one or the other

side of the abdomen. Such a condition plainly demands urologic and urographic examination.

The most common roentgenographic and urographic observations in making the diagnosis of large solitary cyst of the kidney are as follows: (1) compression of the renal pelvis or of one or more calices; (2) change in the position of the axis of the kidney; (3) inward displacement of the ureter; (4) displacement or rotation of the renal pelvis, upward or downward; (5) visualization of the shadow of the cyst; (6) crescent shape of the kidney pelvis or of a calix; (7) calcification of the cyst walls in some cases; (8) visibility of the psoas muscle through the walls of the cyst; (9) shadow of the cyst superimposed on the kidney shadow; (10) visualization of the cyst furnished by pyelovenous backflow.

While this benign localized lesion has in the past been considered harmless, experience shows that from time to time cases are encountered in which a malignant tumor is concealed within the walls of the cyst. This fact justifies the insistence on open surgical exploration to verify the diagnosis and on removal of the cyst by conservative operation when possible or radical procedure when necessary, not only to prevent further symptoms but also to remove any possibility of extension of a malignant growth. With a tumor of the kidney, the pyelogram as a rule shows more marked invasion of the calices and the renal pelvis, since the growth of the tumor extends inward to occupy the renal parenchyma, while the cyst tends to spread outward. A pyelogram of a tumor of the kidney presents a more disorganized and more bizarre appearance, following no such rule of uniformity as that of a large simple cyst. Furthermore, in the case of such a cyst the shadow of the kidney itself is usually not enlarged, whereas the shadow of the kidney is considerably increased if there is a malignant tumor of that organ.

In this series of 10 cases, 4 patients were operated on, with curative results. In 1 case the operation was resection of the cyst from the upper pole followed by right nephropexy. In 2 cases extraperitoneal lumbar nephrectomy was done and in 1 a transperitoneal nephrectomy, all with gratifying results. Of the 6 patients not operated on, 3 were improved, and 3 were not followed up.

The youngest patient was a woman 18 years of age and the oldest a man 74. There were 5 women and 5 men. The diagnosis in 4 cases was made by intravenous urography and in 4 others by retrograde pyelograms. In the 2 remaining cases urography failed to reveal the cyst, and the diagnosis was made during operation for nephropexy.

The cyst was located in the upper pole of the right kidney in 2 cases, in the upper pole of the left kidney in 2, in the lower pole of the right kidney in 3 and in the lower pole of the left kidney in 3.

It was striking to note that in the 2 cases in which the diagnosis was not made before operation the patients were women in whom the right kidneys were low in position and readily palpable on physical examination and the urographic studies revealed marked pyelectasis, caliectasis and evidence of pyelonephritis and right nephroptosis. In 1 of these 2 cases, the cyst was in the upper pole of the right kidney, and in the other, in the lower pole. In the first of these (case 1) resection of the upper pole of the right kidney followed by nephropexy relieved all symptoms and resulted in the permanent cure of a patient who had had two abdominal operations ten and twelve years previously for the same symptoms, both times without relief. In the other case (case 3), owing to anomalies of the blood supply, nephrectomy was necessary and resulted in cure.

In case 2 of this series a diagnosis of left renal neoplasm had been made elsewhere for the patient, who had marked hypertension and an attack of painless hematuria. However, according to my urographic findings the preoperative diagnosis was large serous cyst of the upper pole of the left kidney, and this was confirmed at operation.

Case 4 is a vivid illustration of the possibility of a large solitary cyst of the kidney enclosing a malignant growth within its walls. The patient was a girl 18 years of age, who had undergone exploratory laparotomy elsewhere; at that time the appendix and a small ovarian cyst had been removed. About a year later, after injury from a fall, acute abdominal symptoms developed. She was then hospitalized and submitted to urographic examination which disclosed a gigantic cyst at the upper pole of the right kidney. The cyst was removed by transperitoneal nephrectomy. Examination of the specimen disclosed Wilms's tumor within the cyst.

In case 7 the diagnosis of large solitary renal cyst was made by intravenous urography and confirmed by puncture and aspiration of the fluid. On the first puncture 120 cc. of clear fluid was aspirated, and on the second puncture, one year later, 750 cc. The aspirated fluid, which was of clear amber color, contained no urea, but the actual lesion underlying the cyst remained unknown for lack of surgical approach.

In the remaining 5 cases the diagnosis was definitely made urographically and substantiated by clinical observation, although in none of these cases was operation performed.

Finally, it appears that when there are enough urologic symptoms and when the preoperative urographic diagnosis has been made, the ideal course is to advise open surgical exploration of the kidney and the cyst by laparotomy with a view to resection of the cyst by one of the conservative operations described, in order to save the kidney and eliminate all possible complications or further disease that may jeopardize

the life of the organ. Even in borderline cases this appears to be the safest course. Then, in cases in which the kidney cannot be saved by conservative surgical procedures, nephrectomy will still remain as a last resort.

Drs. F. B. Lopez of Habana, Cuba, E. J. Daly of Jersey City, N. J., and J. W. Draper of New York Hospital permitted the report of cases 3, 4 and 7, respectively. Dr. H. R. Muller of Doctors Hospital made the histologic sections in case 2, of which photomicrographs are presented.

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EFFECT OF ASPHYXIA CAUSED BY BOWEL DISTENTION ON THE CONCENTRATION OF THE BLOOD

W. D. GATCH, M.D.

AND

J. S. BATTERSBY, M.D.

INDIANAPOLIS

Fine¹ and associates showed that bowel distention maintained for many hours causes marked concentration of the blood. They asserted that this cannot be explained by dehydration or by intraperitoneal loss of fluid. In their most recent publication they stated that they have been unable to account for it.² (We have repeated many of their experiments with results the same as they reported.) In our other paper³ on this general subject we presented experimental and clinical findings which showed that the intraperitoneal loss of blood protein is considerable when the bowel is inflated by pressures which we believe act on the human bowel in cases of acute obstruction. We observed some local loss when we used the pressures which Fine employed. However, this loss is not sufficient in most cases to account for the great concentration of the blood which occurs after prolonged inflation of the intestine. Further, this concentration occurs even when the pressure used is too low to damage the bowel. We planned the experiments hereinafter described to discover what causes this concentration of the blood.

PROTOCOLS OF EXPERIMENTS

SERIES 1 (6 dogs).—*Experiments to Show the General Effects of Prolonged Distention of the Bowel.*—Sodium amytal (50 mg. per kilogram of body weight) was given intravenously to produce light anesthesia. Laparotomy was done, and ligatures were applied to the pylorus and the ileocecal valve over the tubes which had been introduced into the intestine at these points. The bowel was inflated in various experiments with pressures ranging from 22 to 96 mm. of mercury. One pressure was used in each experiment. The pressure was maintained until the

1. Gendel, S., and Fine, J.: The Effect of Acute Intestinal Obstruction on the Blood and Plasma Volume, *Ann. Surg.* **110**:25-36, 1939.

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3. Gatch, W. D., and Battersby, J. S.: The Two Stages of Bowel Distention: A Study of Bowel Injury by Distention and Its Effect on Volume and Concentration of Blood, *Arch. Surg.* **44**:108-118 (Jan.) 1942.

dog died or showed unmistakable signs of the effects of the pressure. Blood pressures of some of these dogs were taken.

Results.—The blood pressure did not fall to a significant extent until shortly before death. Marked cyanosis of the mucous membranes developed in all the animals. The respiratory rate always increased, and the breathing became shallower as time passed. The higher pressures caused death much sooner than the lower.

Autopsy.—The quantity of fluid present in the peritoneal cavity was considerable in those dogs in which the higher pressures had been used. In these dogs gross signs of injury to the bowel were present in the form of subperitoneal hemorrhages, matting together of loops of bowel and albuminous exudate. The spleen was always hard and contracted. The bladder usually contained 100 to 150 cc. of urine. The heart, the lungs, the kidneys, the muscles and the subcutaneous tissues were normal. The most striking findings were general cyanosis and a tarry consistency of the blood.

SERIES 2 (4 dogs).—Experiments to Determine Whether Nervous Impulses⁴ Caused by Distention of the Bowel or Toxic Substances Absorbed from the Damaged Bowel Are Responsible for the Concentration of the Blood.—The same procedures were employed as in series 1 except that all the blood vessels of the small intestine were divided between ligatures. In two experiments the entire small bowel was removed, and strips of Penrose tubing, 1 inch (2.5 cm.) in diameter and equal in combined length to the excised intestine, were then placed within the abdomen and inflated with a pressure equal to that used in the experiments on the intestine.

Results.—The results of these experiments were the same as those obtained in series 1.

SERIES 3 (3 dogs).—Experiments to Determine Whether Inflation of the Stomach Has the Same Effect as Inflation of the Bowel.—The same procedures were used as in series 1 except that ligatures were applied to the cardiac and the pyloric ends of the stomach, which was then inflated. In two experiments the stomach was inflated with a maintained pressure of 22 mm. of mercury. This caused the death of both dogs within three hours. At autopsy the stomach was observed to fill the entire abdomen in both dogs. In neither dog, however, did it show any gross sign of injury other than this marked distention, and in both it contracted considerably on deflation.

In a third experiment the stomach of a dog was inflated with a maintained pressure of only 15 mm. of mercury. This dog was killed at the end of six hours, when it was in a moribund condition. Its stomach was not so markedly distended as those of the other 2 dogs.

Results.—In general the results were the same as those in series 1 except that the animals died much sooner, there was no free fluid in the abdomen and the blood concentration was not so great. We found no fluid in the stomach or the peritoneal cavity of any of these dogs. Blood determinations obtained in this series are given in table 1.

4. Fine, J.; Rosenfeld, L., and Gendel, S.: The Role of the Nervous System in Acute Intestinal Obstruction, *Ann. Surg.* **110**:411-416, 1939.

Conclusions.—The results of the experiments described show: (1) that distention of the bowel and distention of the stomach cause the death of the experimental animal under anesthesia induced by sodium amytal in a period of time which varies inversely with the amount of pressure used to distend the intestine or the stomach; (2) that concentration of the blood occurs; (3) that this concentration when low pressure is used can only in part be accounted for by the loss of fluid in the peritoneal cavity or by way of the kidneys, the bowel or the lungs.

The only explanation of this loss which we can conceive is that it is caused by the escape of blood proteins from capillaries in all parts of the body. This implies that distention of the bowel in some way injures the capillary endothelium of the body and permits the blood proteins to escape.

TABLE 1.—*Blood Determinations of the Dogs Submitted to Gastric Distention*

Dog	Weight, Kg.	Pressure Used in Gastric Distention, Mm. of Mercury	Oxygen Content of the Venous Blood, Volumes per Cent		Hematocrit Determinations per Cent		Duration, Hr.
			Normal	Final	Normal	Final	
1	8.6	22	17.3	3.9	46	50	3 (death)
2	14.1	22	16.7	12.3	42	49	3 (death)
3	13.6	15	11.5	8.1	53	70	6

Analysis of the blood after prolonged distention of the bowel shows that it has lost much more albumin than globulin. This indicates that the damage to the capillary endothelium is not so grave as that caused by burns or inflammation, since after these injuries the large globulin molecules escape as easily as the smaller albumin molecules. Further, it is well established that the experimental animal can recover from the effects of distention of the bowel if this has not been too prolonged. The results of the foregoing experiments make it inconceivable that distention of the bowel causes capillary damage by any neural mechanism or by the action of any toxic material produced in the distended bowel. These considerations led us to make the hypothesis that the damage to the capillaries is due to slowly developing asphyxia caused by distention of the bowel or stomach.

SERIES 4.—Experiments to Determine the Effect of Distention of the Bowel on the Oxygen Content of Arterial and Venous Blood, as Well as the Effect on the Circulation Time.—In this series hematocrit and venous and arterial blood oxygen determinations were made after distention of the bowel. The effect of distention

on the blood circulation time was ascertained by the sodium cyanide method; 0.5 mg. of sodium cyanide per kilogram of body weight was used.

Results.—The results of two experiments in this series are given in figure 1.

It is generally agreed that anoxia damages the endothelium.⁵ How does distention of the bowel cause anoxia? Can anoxia alone cause blood concentration, and will the findings at autopsy be identical with those caused by distention of the bowel? The experiments in series 5, 6 and 7 were performed to answer these questions.

SERIES 5 (4 dogs).—Experiments to Determine Whether Artificial Respiration or the Respiration of Pure Oxygen Can Prevent the Blood Concentration Caused

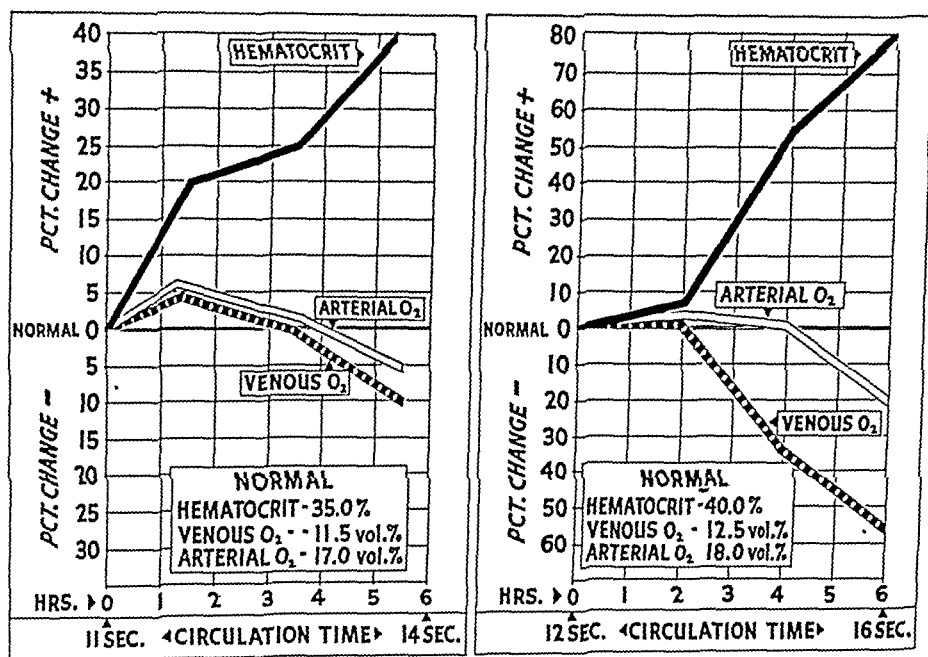


Fig. 1.—The effect of distention of the bowel on the oxygen content and circulation time of the blood.

by Distention of the Bowel.—The procedures were the same as in series 1 except that tracheotomy was done to facilitate artificial respiration and to administer pure oxygen. Artificial respiration was carried out on 2 dogs at the rate of 20 respirations a minute, and the quantity of air used to inflate the lungs of each dog was equal to the tidal air of the animal at the beginning of the experiment. A mercury manometer was connected with the apparatus to make sure that the lung was never inflated with a pressure greater than 6 mm. of mercury. The

5. Landis, E. M.: Micro Injection Studies of Capillary Permeability: III. The Effect of Lack of Oxygen on the Permeability of the Capillary Wall to Fluid and to Plasma Protein, *Am. J. Physiol.* 83:528-542, 1928.

dogs given pure oxygen were not submitted to artificial respiration. The intra-intestinal pressure used in all cases was 29 mm. of mercury.

Results.—The results are shown in table 2.

Conclusions.—Our conclusions from this series of experiments are: (1) that both artificial respiration and the administration of pure oxygen prolong the life of animals with distention of the bowel; (2) that both oppose but do not prevent blood concentration in animals with distention of the bowel; (3) that both mitigate but do not prevent asphyxia.

TABLE 2.—*Effects of Artificial Respiration and the Inhalation of Pure Oxygen on the Blood Concentration Caused by Distention of the Bowel*

Dog	Weight, Kg.	Pressure of Inflation, Mm. of Mercury	Oxygen Content of the Venous Blood, Volumes per Cent		Hematocrit Determination, per Cent		Duration, Hr.	Oxygen Capacity of the Venous Blood, Volumes per Cent	
			Normal	Final	Normal	Final		Normal	Final
A. Artificial Respiration *									
1	15.7	29	10.5	7.8	49	57	7		
2	15.0	29	10.0	7.5	39	69	16	14.5	20.5
B. Inhalation of Pure Oxygen									
3	16.3	29	15.6	10.9	45	58	5	20.0	27.2
4	14.1	29	16.4	12.6	38	54	6	18.3	22.3

* Artificial respiration was administered at the rate of 20 respirations per minute; the volume of tidal air was normal.

TABLE 3.—*Effect of Asphyxia Caused by Limiting the Volume of Tidal Air on the Blood Picture*

Dog	Weight, Kg.	Respirations per Minute	Tidal Air	Hematocrit Determination, per Cent		Duration, Hr.	Oxygen Content of the Venous Blood, Volumes per Cent	
				Initial	Final		Initial	Final
1	14.0	40	..	47	60	6	15.7	9.9
2	14.1	..	½	42	39	3 (death)	16.7	12.3
3	8.6	50	..	52	61	7	18.0	12.5

SERIES 6 (3 dogs).—*Experiments to Determine Whether a Moderate Degree of Asphyxia Produced by Limiting the Air Supplied to the Lungs Causes the Same Blood Picture and Presents the Same Changes at Autopsy as Distention of the Bowel.*—Sodium amytal (50 mg. per kilogram of body weight) was used to induce anesthesia. Tracheotomy was performed. Determination of the tidal air was made. Limitation was imposed on the tidal air, but in no case was this decreased by more than one half of its normal volume.

Results.—The results are given in table 3.

Conclusion.—Moderate and prolonged asphyxia caused by limiting the volume of the tidal air will produce the same blood picture and will present identical changes at autopsy as distention of the bowel.

SERIES 7 (6 dogs).—*Experiments to Determine the Systemic Effect of Distention Limited to Separate Parts of the Gastrointestinal Tract.*—Sodium amytal was used to induce anesthesia. Fluoroscopic examination was made of the thorax to determine the effects of (1) inflation of the stomach, (2) inflation of the entire small bowel and (3) inflation of the large bowel. The pressure used in all experiments was 29 mm. of mercury. We observed that inflation of the stomach caused marked elevation of the diaphragm, that inflation of the small bowel caused lesser elevation and that inflation of the large bowel caused no elevation.

We observed also that after inflation of the stomach or the small bowel there was a marked decrease in the movement of the ribs and a great increase in the rate of respiration.

In two experiments we measured the volume of the tidal air and recorded the rate of respiration while the small bowel was kept inflated with a pressure of 29 mm. of mercury.

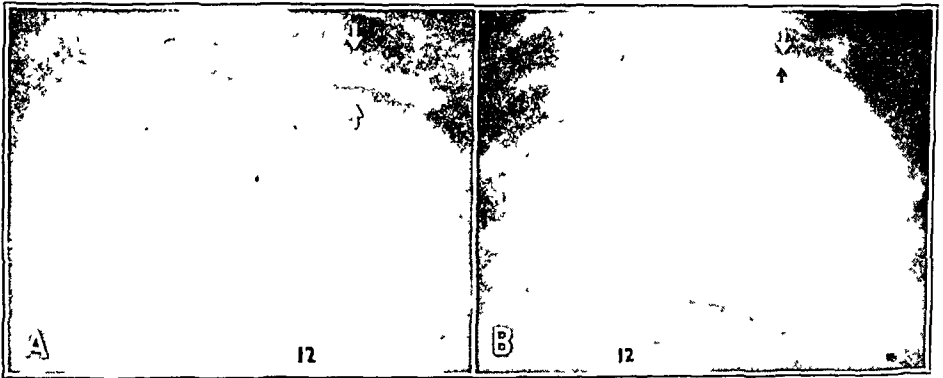


Fig. 2.—The effect of distention on the elevation and excursion of the diaphragm. *A*, normal; *B*, intestinal distention with elevation and limitation in the range of excursion.

TABLE 4.—*Effects of Distention Limited to the Small Bowel on the Respiration of a Dog*

Time of Determination	Respirations per Minute	Volume of Tidal Air, Cc.	Volume of Air Breathed per Minute, Cc.
Start.....	12	83	996
3 hours.....	26	90	2,340
6 hours.....	34	50	1,700

Results.—Results of one of the experiments are shown in table 4.

Despite the increased volume of air which these animals breathed, the oxygen in their blood steadily decreased, for their mucous membranes became more and more cyanotic. The truth of this observa-

tion is confirmed by the measurements made under similar conditions of the oxygen content of the venous and arterial blood of the animals in series 4.

We have shown (series 5) that neither artificial respiration nor the administration of pure oxygen can cause efficient oxygenation of the blood of animals with distention of the bowel. The demonstration of this effect of distention is sufficient for our present purpose; we plan a special study of its causes.

COMMENT

We conclude that asphyxia is the primary cause of death after prolonged distention of the stomach or small intestine. Concentration of the blood while distention is present is due to damage to the capillary endothelium of all parts of the body caused by the lack of oxygen.

It seems clear that asphyxia causes hemoconcentration and that hemoconcentration increases asphyxia. In two experiments in which the entire small bowel was inflated for eight hours we were able to prevent hemoconcentration by giving intravenously 100 cc. of plasma per hour. Both animals were in good condition at the end of this period. The experiments were ended because the supply of plasma was used up. Hemoconcentration is an important but secondary cause of death from distention. Asphyxia due to distention can cause death in the absence of serious hemoconcentration. We proved this at least for distention of the stomach.

Effects of distention similar to these in experimental animals must occur in human beings, but we are not as yet prepared to state how important they are in clinical practice.⁶ Everyday experience in the laboratory shows that the dog is more quickly injured by interference with respiration than man.⁷ The dire results of distention of the stomach are well known, and it seems probable to us that the mechanism we have studied is responsible for them.

While we have been engaged in this experimental work, we have observed several patients suffering from prolonged distention of the small bowel. In none of them did we observe concentration of the blood though none of them had been given blood or plasma. All, however, had continuous gastric lavage.

We recall seeing many patients who were suffering from severe embarrassment of respiration because of acute and rapidly developing

6. Fine, J.; Hurwitz, A., and Mark, J.: Clinical Study of Plasma Volume in Acute Intestinal Obstruction, *Ann. Surg.* **112**:546-556, 1940.

7. Gatch, W. D.; Mann, F. C., and Gann, D.: The Danger and Prevention of Severe Cardiac Strain During Anaesthesia, *J. A. M. A.* **60**:1273-1278 (April 26) 1913.

distention. This work should at least make us look for hemoconcentration in all patients with obstruction of the bowel and, if we find it, give plasma in adequate quantities.

CONCLUSIONS

Prolonged distention of the stomach and the small bowel with pressures too low to damage them results in death of the experimental animal. Asphyxia due to interference with respiration is the cause of death.

All the effects of distention can be produced by prolonged limitation of the air supply.

The blood concentration observed in these experiments is a result of, and aggravates, asphyxia, but is not the primary cause of death, which may occur without much concentration of the blood. Death is delayed when blood concentration is prevented by the administration of adequate quantities of plasma.

Distention of the stomach is more rapidly fatal than distention of the small bowel; distention of the large bowel is comparatively harmless. These effects depend on the degree of interference with respiration caused by distention of these parts of the gastrointestinal tract.

The full clinical importance of these experimental observations has not been determined.

MATERIALS FOR INTERNAL FIXATION OF INTRACAPSULAR FRACTURE OF THE NECK OF THE FEMUR

EDWARD L. COMPERE, M.D.

CHICAGO

GEORGE WALLACE, M.D.

ROCHESTER, MINN.

AND

JOHN LEE, M.D.

LOS ANGELES

The advantages of internal fixation of fractures of the intracapsular neck of the femur as compared with less satisfactory methods of immobilization formerly widely used are acknowledged by most orthopedic surgeons and by those general or traumatic surgeons who are sufficiently trained in the discipline of aseptic surgery and the principles of the healing of fractures to be able to apply with skill and judgment one of the many widely described technics. The confusion today is concerned primarily with the fact that each of many surgeons has designed, used and recommended his own variation of wire, pin, screw or gadget for maintaining position after reduction of a fracture of the femoral neck.

Much of the widespread interest in internal fixation of fractures of the hip must be credited to Smith-Petersen,¹ who described, used successfully and popularized the three-flanged nail.

The average incidence of union from all methods of internal fixation, including small nails,² small threaded pins or wires,³ larger smooth pins,⁴

From the Department of Surgery, University of Chicago.

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2. Moore, A. T.: Fracture of the Hip Joint (Intracapsular): A New Method of Skeletal Fixation, *J. South Carolina M. A.* **30**:199-205 (Oct.) 1934; Fractures of the Neck of the Femur, *South. Surgeon* **8**:139-147 (April) 1939; Fracture of the Hip Joint, *Surg., Gynec. & Obst.* **64**:420-436 (Feb., no. 2 A) 1937.

3. Compere, E. L., and Lee, J.: The Restoration of Physiological and Anatomical Function in Old Ununited Intracapsular Fractures of the Neck of the Femur, *J. Bone & Joint Surg.* **22**:261-277 (April) 1940. Compere, E. L.: The

(Footnotes continued on next page)

two-flanged⁵ or three-flanged nails,⁶ small screws,⁷ large screws,⁸ the lag screw⁹ and other pins or spikes,¹⁰ has been greater than 80 per cent. After experience with several different types of the materials most commonly used, including the Smith-Petersen nail, it became obvious to us that there were both disadvantages, in part theoretic and in part practical, and certain advantages to be obtained from each.

Theoretically, the ideal method for the internal fixation of intracapsular fracture of the neck of the femur should meet the following requirements: (1) Immobilization should be sufficiently well maintained to prevent refracture, angulation at the site of fracture or displacement with separation of fracture fragments. (2) The internal fixation should be sufficient in itself so that neither plaster cast nor long immobilization in bed following reduction and fixation will be necessary. (3) Intact nutrient arteries in the neck or the head of the femur should not be endangered by the forceful insertion of chisels or even of a nail or a screw which is greater in diameter than is really essential for maintaining immobilization. (4) The pin, screw or nail selected should not needlessly displace cancellous bone and should not grossly obstruct attempts at revascularization. (5) Materials used for immobilization should obtain a sufficient degree of fixation so that they will neither migrate

Ambulatory Treatment of Recent Fractures of the Intracapsular Neck of the Femur Following Threaded Wire Fixation, *J. Internat. Coll. Surgeons* **3**:401-410 (Oct.) 1940. Telson, D. R., and Ransohoff, N. S.: Treatment of Fractured Neck of the Femur by Axial Fixation with Steel Wires, *J. Bone & Joint Surg.* **17**:727-738 (July) 1935.

4. Sofield, H. A.: Fracture of the Neck of the Femur Treated by the Steel Pin Method of Fixation, *Illinois M. J.* **71**:200-204 (March) 1937.

5. Cubbins, W. R.; Callahan, J. J., and Scuderi, C. S.: Fractures of Neck of Femur; Open Operation and Pathologic Observations; New Incision and New Director for Use of Simplified Flange, *Surg., Gynec. & Obst.* **68**:87-94 (Jan.) 1939.

6. Campbell, W. C.: Internal Fixation in Fractures of the Neck of the Femur, *Ann. Surg.* **105**:939-952 (June) 1937. Smith-Petersen, Cave and Vangorder.¹

7. Thomas, T. T.: Fixation by a Wood Screw Without Arthrotomy in Certain Fractures of the Neck of the Femur, *Am. J. Surg.* **35**:292-295 (Sept.) 1921.

8. Lippmann, R. K.: Corkscrew-Bolt for Compression-Fixation of Femoral Neck Fractures, *Am. J. Surg.* **37**:79-87 (July) 1937.

9. Henderson, M. S.: Internal Fixation for Recent Fractures of Neck of Femur, *S. Clin. North America* **19**:927-942 (Aug.) 1939.

10. Gaenslen, F. J.: Subcutaneous Spike Fixation of Fresh Fractures of Neck of Femur, *J. Bone & Joint Surg.* **17**:739-747 (July) 1935; Fracture of the Neck of the Femur, *J. A. M. A.* **107**:105-114 (July 11) 1936. Wescott, H. H.: A Method for the Internal Fixation of Transcervical Fractures of the Femur, *Virginia M. Monthly* **59**:197-204 (July) 1932; Method for Internal Fixation of Transcervical Fractures of Femur, *J. Bone & Joint Surg.* **16**:372-378 (April) 1934. Knowles, F. L.: Fractures of the Neck of the Femur, *Wisconsin M. J.* **35**:106-109 (Feb.) 1936.

forward into the acetabulum and the pelvis (as has happened in too many cases in which small smooth pins or wires have been used) nor become loosened and displaced outward as the patient becomes active and ambulatory on crutches, because immobilization would thus be lost and nonunion result.

One of us (Compere³) has reported aseptic necrosis of the head of the femur following the insertion of a Smith-Petersen nail, although union of the fracture was obtained. This has also been demonstrated by Campbell,⁶ and the role played by the nail through possible injury to nutrient blood vessels or through prevention of revascularization during the months in which the three blades of the nail remained in situ has been postulated.

Our early experience in the use of Kirschner wires was most unsatisfactory because when the patients were permitted to become ambulatory on crutches, several or all of the wires became dislodged and migrated outward. This has also been the experience of others.¹¹

The purpose of this study has not been to compare by test all of the many varieties of pins, nails, screws or gadgets. Reports of the successful use of small, threaded, drill point, stainless steel wires and the theoretic reasons for our choice of this method of internal fixation of fractures of the intracapsular neck of the femur have been included in earlier papers.³

The question which we have tried to answer has been merely this: Is it possible to obtain uniformly satisfactory immobilization of an intracapsular fracture of the neck of the femur through the use of three highly tempered stainless steel wires, gage .080, with fifty-six threads to the inch (2.5 cm.)?

We undertook to study the breakdown force of hips obtained at necropsy, fractured and pinned with three of the threaded wires. Later, the distraction force, or the pull in pounds required to separate completely the fracture fragments after pinning, was also studied. It then seemed advisable to learn whether the three threaded wires compared favorably in efficiency with the more widely used flanged nails or the stronger but nonthreaded round pins or nails. We selected the Smith-Petersen three-flanged nail and the nonthreaded round Steinman pins for comparison because of their known tensile strength.

PROCEDURE

Arrangements were made to obtain the entire proximal end of each femur of patients subjected to necropsy at the Cook County Infirmary. The postmortem examinations were performed from three to seventeen days after death; the average time was eight days. Some of the patients from whom these specimens were obtained had been bedridden or in a wheel chair for several months to as long

11. Selig, S.: Objections to the Use of Kirschner Wire for Fixation of Femoral-Neck Fractures, *J. Bone & Joint Surg.* **21**:182-186 (Jan.) 1939.

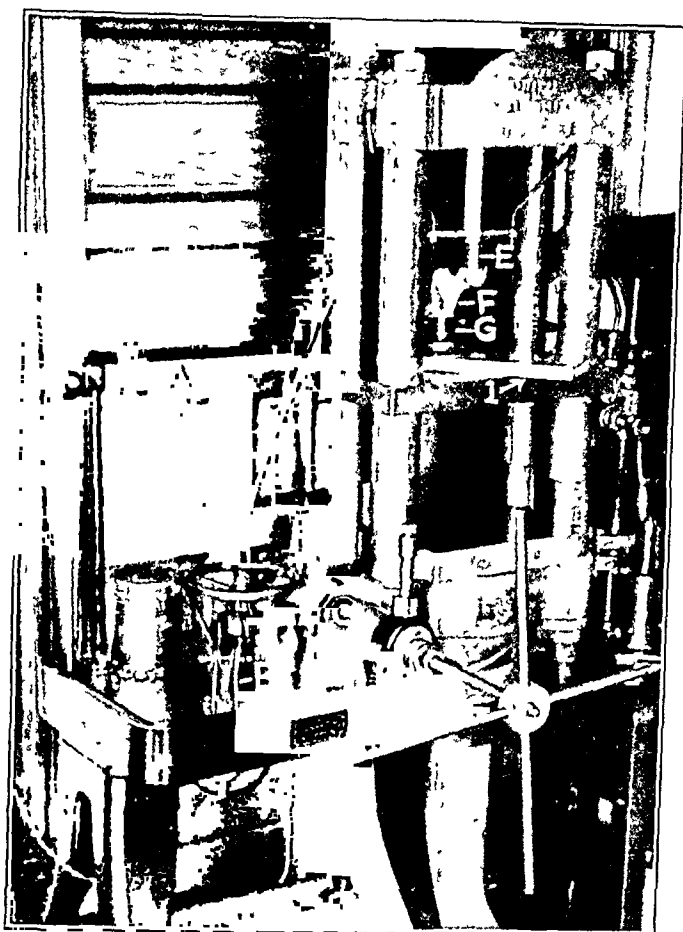


Fig. 1.—Machine used for testing fracture and breakdown forces: *A*, scale (weight balance); *B*, revolving motor-driven piston; *C*, hand-worked pressure cylinder; *E*, plaster cap over femoral head to prevent point pressure; *F*, a fresh femoral head, neck and trochanters; *G*, the shaft of the femur embedded in plaster in a metal cup; *I*, oak plank.

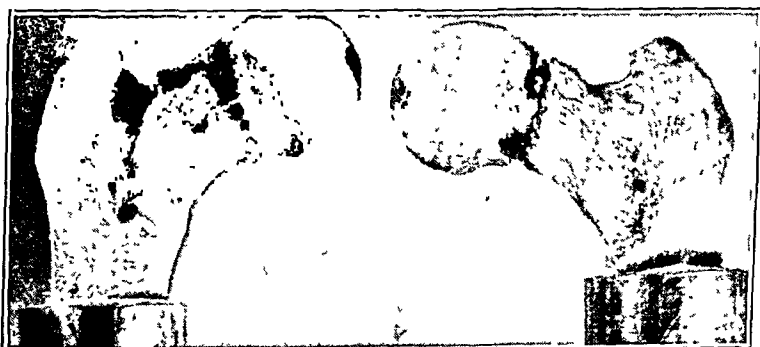


Fig. 2.—Photograph of two hips obtained at necropsy, mounted in plaster cups and then fractured by direct pressure force.

as nine years prior to death. Most of them had been elderly. The bone in the region of the neck of the femur was therefore atrophied from disuse, even to a greater extent than that which is usually found in a patient who has been sufficiently active to be ambulatory at the time of sustaining a clinical fracture. The hips were freed of all soft tissue attachments with a minimal amount of trauma to the periosteum. Neither dissolving, decalcifying nor fixating chemicals were used. Each hip was mounted in a round metal cylinder, approximately 5 cm. in diameter, and fresh plaster of paris was poured around the shaft. A second, concave mold



Fig. 3.—Roentgenogram of the hips of a 51 year old laborer who was ambulatory until one week before death, showing the position of the three threaded wires after pinning of the fracture fragments

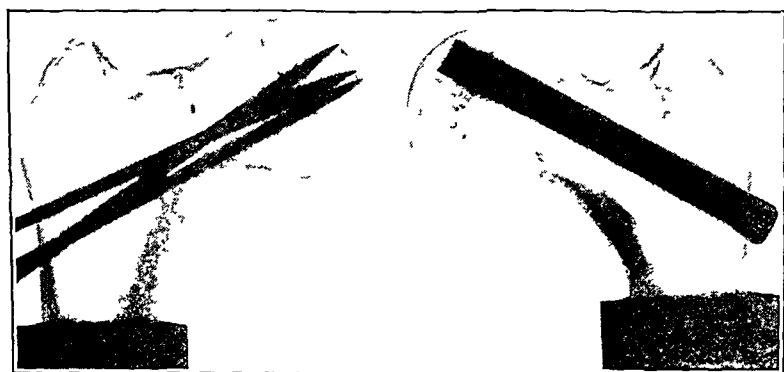


Fig. 4.—Roentgenogram of the hips of a 54 year old laborer who had been bed-ridden for several months before fracture, taken after reduction and pinning of the left hip with three Steinman pins and of the right hip with a Smith-Petersen nail.

was applied over the head of the femur so that force could be directed against the femoral head over a wide surface and local infraction be avoided.

Study of the fracture force and subsequently of the breakdown force after pinning was made possible through the aid of Dr. J. J. Prochaska and the Illinois Institute of Technology. The machine used for creating the fracture force was a hydraulic press designed for testing the tensile strength of wood and metals (fig. 1). The concave plaster cap was brought down with increasing force on the head of the femur until a fracture occurred (fig. 2). In some instances the fracture was subcapital, but in most of the experiments the fracture line was

oblique from the superior edge of the head downward and laterally toward the lesser trochanter. The number of pounds of pressure required to produce the fracture was recorded in each instance; this we have described as the fracture force. The fractured hips were repinned in as nearly anatomic position as possible (fig. 3).

TABLE 1.—*Data on Cases in Which Three Threaded Wires Were Introduced into Each Hip After Fracture*

Case	Hip	Fracture Force		Breakdown Force		Comment
		Lb.	Kg.	Lb.	Kg.	
1	Right	1,408	638.7	690	313	The patient was a 69 yr. old laborer; weight, 120 lb. (54.4 Kg.); ambulatory to day of death; acute hemorrhage into myocardium
	Left	1,640	743.9	1,488	674.9	
2	Right	680	308.4	460	217.7	The patient was an 89 yr. old housewife; weight 90 lb. (40.8 Kg.); bedridden six months; multilobular empyema
	Left	904	410	510	231.3	
3	Right	2,340	1,061.4	768	348.4	The patient was a 78 yr. old laborer; weight, 160 lb. (72.6 Kg.); ambulatory until four days before death; coronary thrombosis
	Left	2,208	1,001.5	558	258.1	
4	Right	2,400	1,088.6	252	114.3	The patient was a 51 yr. old laborer; weight 140 lb. (63.5 Kg.); ambulatory until a week before death; syphilitic aortic aneurysm and bronchopneumonia
	Left	2,460	1,115.8	432	196	
5	Right	564	255.8	186	84.4	The patient was a 67 yr. old laborer; weight, 130 lb. (59 Kg.); bedridden two months; old mid-thigh amputation on right side; right femur atrophied from disuse; arteriosclerotic cardiovascular disease; hypostatic pneumonia
	Left	1,674	759.3	872	168.7	
6	Right	1,728	783.8	420	190.5	The patient was a 53 yr. old laborer; weight, 135 lb. (61.2 Kg.); bedridden one month; cancer of the rectum with metastasis
	Left	1,638	742	360	163.2	
7	Left	2,220	1,007	330	149.6	The patient was a 44 yr. old man, a cook; weight, 120 lb. (54.4 Kg.); ambulatory until two days before death; massive bilateral fibroid tuberculosis
8	Left	1,140	517	300	136	The patient was a 64 yr. old printer; weight, 75 lb. (34 Kg.); in bed three months before death; anatomic diagnosis: pernicious anemia, healed pulmonary tuberculosis, multiple diverticula of small bowel
9	Left	1,440	653	320	145.1	The patient was a 42 yr. old man; weight, 100 lb. (45.4 Kg.) in wheel chair many months before death; unilateral pulmonary tuberculosis
10	Left	2,019	915.4	330	149.6	The patient was a 61 yr. old laborer; weight, 165 lb. (74.8 Kg.); bedridden period unknown; arteriosclerotic cardiac disease and generalized arteriosclerosis
11	Right	2,100	952.5	330	149.6	The patient was a 46 yr. old switchman; weight, 130 lb. (59 Kg.); bedridden seven months cirrhosis of the liver and mucous colitis
12	Left	1,260	571.5	270	122.5	The patient was a 49 yr. old laborer; weight, 112 lb. (50.8 Kg.); ambulatory until death; anatomic diagnosis: bilateral pulmonary fibroid tuberculosis and bilateral tuberculous pleuritis
13	Left	1,620	734.8	240	108.8	The patient was a 72 yr. old man; weight, 100 lb. (45.4 Kg.); ambulatory until two months before death; hypertensive cardiac disease and generalized arteriosclerosis
Average		1,655	750.7	455	206.4	

Nineteen hips were pinned with threaded wires, 5 with Steinman pins and 4 with a Smith-Petersen nail (fig. 4).

RESULTS

The results of these tests are shown in tables 1, 2 and 3. The threaded wires compared favorably with the larger nail or pins in resisting the breakdown force.

The wires were inserted transversely in one hip and obliquely from below upward in the other hip from each of 6 consecutive necropsies. We were surprised to find that the wires placed transversely resisted the

TABLE 2.—*Data on Cases in Which Three Steinman Pins Were Introduced into Each Hip After Fracture*

Case	Hip	Fracture Force		Breakdown Force		Comment
		Lb.	Kg.	Lb.	Kg.	
1	Left	1,344	609.6	152	68.9	The patient was a 54 yr. old laborer; weight, 120 lb. (54.4 Kg.); bedridden several months; pelvic neoplasm and bronchopneumonia
2	Right	2,760	1,251.9	480	217.7	The patient was a 61 yr. old laborer; weight, 165 lb. (74.8 Kg.); bedridden period unknown; arteriosclerotic cardiac disease and generalized arteriosclerosis
3	Left	1,800	816.5	270	122.5	The patient was a 46 yr. old switchman; weight, 130 lb. (59 Kg.); bedridden seven months; cirrhosis of the liver and mucous colitis
4	Right	1,320	598.7	360	163.2	The patient was a 49 yr. old laborer; weight, 112 lb. (50.8 Kg.); ambulatory until death; anatomic diagnosis: bilateral pulmonary fibroid tuberculosis and bilateral tuberculous pleuritis
5	Right	1,620	734.8	600	272.2	The patient was a 72 yr. old laborer; weight, 100 lb. (45.4 Kg.); ambulatory until two months before death; anatomic diagnosis: hypertensive cardiac disease and generalized arteriosclerosis
Average		1,769	802.4	372	168.7	

TABLE 3.—*Data on Cases in Which a Smith-Petersen Nail Was Introduced into Each Hip After Fracture*

Case	Hip	Fracture Force		Breakdown Force		Comment
		Lb.	Kg.	Lb.	Kg.	
1	Right	1,026	465.4	582	264	The patient was a 54 yr. old laborer; weight, 120 lb. (54.4 Kg.); bedridden several months; pelvic neoplasm and bronchopneumonia
2	Right	2,340	1,016	300	136	The patient was a 44 yr. old man; a cook; weight, 120 lb. (54.4 Kg.); ambulatory until two days before death; massive bilateral fibroid tuberculosis
3	Right	1,260	571.5	270	122.5	The patient was a 64 yr. old printer; weight, 75 lb. (34 Kg.); in bed three months before death; anatomic diagnosis: pernicious anemia, healed pulmonary tuberculosis, multiple diverticula of small bowel
4	Right	1,200	544.3	240	108.9	The patient was a 42 yr. old man; weight, 100 lb. (45.4 Kg.); in wheel chair many months before death; anatomic diagnosis: unilateral pulmonary tuberculosis
Average		1,456	660.4	348	157.8	

breakdown force much more effectively than those inserted obliquely. The average breakdown force of 6 hips pinned with wires in the transverse position was 723.6 pounds (328.2 Kg.). For the 6 contralateral hips pinned with obliquely placed wires the breakdown force was 452 pounds (205 Kg.), a difference of 271 pounds (123 Kg.).

In a smaller series of hips the holding power was tested. This was accomplished by calculating the force in pounds required for pulling the

head and the neck of the femur apart at the line of fracture after pinning with the Smith-Petersen nail, three threaded wires or three Steinman pins inserted in the usual crisscross or toe nail fashion (fig. 5). Although the wires were small and the threading fine, the holding power was greater than that of either the Smith-Petersen nail or the three large Steinman pins (table 4). This would tend to confirm our previous clinical observations that threaded wires which do not taper but maintain a uniform diameter throughout their length obtain a better grasp of the

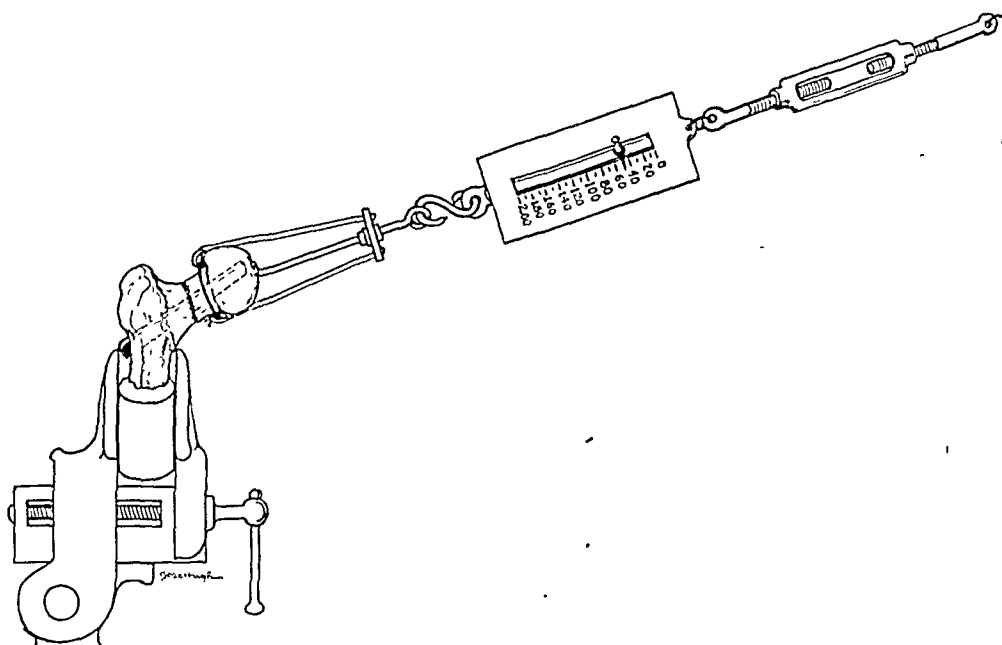


Fig. 5.—Diagrammatic illustration of the method of determining the distraction force required to separate the fracture fragments after pinning.

TABLE 4.—Comparative Holding Power of Nails, Pins and Wires

		Age of Patient, Yr.	Distraction Force **, <div>Lb. Kg.</div>	
Smith-Petersen nail				
Case 1.....	Left	72	70	31.8
Case 2.....	Right	72	60	27.2
Case 3.....	Right	54	20	9.1
Average.....			50	22.7
Three Steinman pins				
Case 1.....	Right	53	63	28.6
Case 2.....	Right	?	20	9.1
Case 3.....	Left	63	147	66.7
	?	?	120	54.4
Average.....			87	39.5
Three threaded wires				
Case 1.....	Right	49	140	63.5
Case 2.....	Right	64	112	50.8
Case 3.....	Left	53	170	77.1
Case 4.....	Right	46	95	43.1
Case 5.....	Left	72	80	36.3
Case 6.....	Right	63	100	45.4
Average.....			116	52.6

* Force required to pull fracture fragments apart after pinning.

bone and show less tendency to migrate than materials which are not threaded (fig. 6). A comparison of threaded wires, Steinman pins and the three-flanged nail as to breakdown resistance and holding power is shown in table 5.

We did not make these tests with Moore nails because they also are threaded where they engage the cortex of the femur, they are of small diameter, and they, too, may be inserted in toe nail fashion. The holding

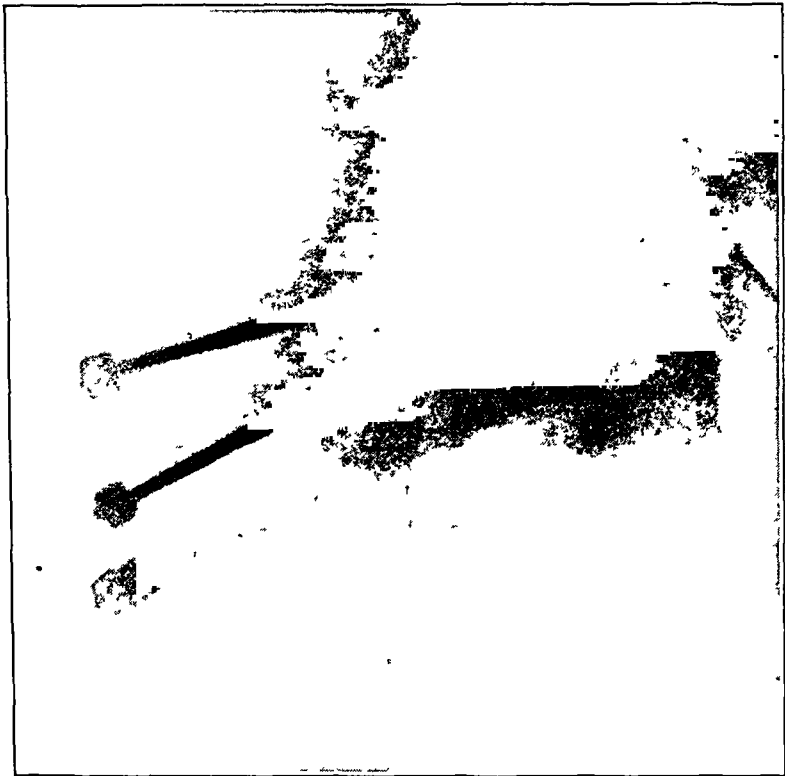


Fig. 6.—Roentgenogram of a hip of a patient aged 71 years after reduction and internal fixation with four threaded steel wires. In each of the breakdown or holding tests the wires remained firm in the femoral head but shredded through the bone of the trochanter and the shaft when the immobilization was disrupted by pressure or by distraction force. For that reason, a round stainless steel nut, illustrated in this roentgenogram, is now used on each wire and tightened firmly against the femoral cortex. When the wire is cut, the threads are flattened, thus holding the nut in place.

TABLE 5.—*A Comparison of the Smith-Petersen Nail, Steinman Pins and Threaded Wires*

	Average Fracture Force		Average Breakdown Force		Average Distraction Force	
	Lb.	Kg.	Lb.	Kg.	Lb.	Kg.
Smith-Petersen nail.....	1,456	660 4	348	157 8	50	22.7
Three Steinman pins.....	1,769	802 4	372	168 7	87	39.5
Threaded wires.....	1,653	750 7	455	206 4	116	52 6

power of Moore nails has been proved by clinical test, and we consider that they are mechanically and theoretically comparable to the threaded wires. We have preferred the wires because of the ease of insertion with a Stille-Scanlon-Kirschner drill. We also suggest that the holding power of the threads on the portion of the wire that enters the head fragment may be of some value in maintaining secure immobilization.

COMMENT

Von Langenbeck¹² was the first to suggest internal fixation of a recent fracture of the neck of the femur, and Koenig¹³ succeeded in nailing such a fracture and reported his results in 1878. In 1889, Senn¹⁴ reported success in the use of a large iron carpenter's nail and taught the principle and advantages of immediate reduction and permanent fixation of a fracture of the neck of the femur by this method. A few years later, Nicolaysen¹⁵ reported with a remarkable degree of modesty a series of 13 successful cases in which he spiked a fractured femoral neck with a three-cornered nail driven directly through the skin but added to this procedure plaster cast immobilization.

The modern surgeon has a wide choice of materials from which to select one for his own uses in pinning fractured hips. The surgeon should first of all be well grounded in the physiology of bone. His responsibility and interest should extend beyond mere healing of the fracture. He should seek to bring about this result with the least possible trauma to the structures with which he is dealing. He should have concern for blood supply to the neck and the head of the femur and guard against doing anything which might increase the hazard of late aseptic necrosis. Devitalization of the head of the femur will nullify an otherwise excellent surgical result, even after union of the fracture has been obtained. A surgeon should think of results in terms of the patient's ability to use the limb with strength, movement and freedom from pain in the years that are to follow treatment.

SUMMARY AND CONCLUSIONS

Three small threaded stainless steel wires accurately placed afford strong immobilization for intracapsular fractures of the neck of the femur. The holding power of three small threaded steel wires is greater than that of the Smith-Petersen nail or of larger, nonthreaded Steinman pins.

12. von Langenbeck: *Verhandl. d. deutsch. Gesellsch. f. Chir.* 7 (pt. 1):92, 1878.

13. Koenig, in discussion on von Langenbeck.¹²

14. Senn, N.: *Treatment of Fractures of the Neck of the Femur by Immediate Reduction and Permanent Fixation*, *J. A. M. A.* 13:150-159 (Aug. 3) 1889.

15. Nicolaysen, J.: *The Diagnosis and Treatment of Fractures of the Neck of the Femur*, *Nord. med. ark.* (no. 16) 8:1-19, 1897.

The insertion of threaded steel wires produces minimal trauma to cancellous bone of the neck or the head of the femur. These wires are unlikely to injure nutrient blood vessels, and they constitute no real obstruction to revascularization. Wires inserted transversely immobilize more securely than those placed obliquely from below upward.

This method has been used successfully both in the treatment of recent fracture of the neck of the femur without any cast and with almost immediate ambulation and also in conjunction with tibial bone grafts in the treatment of old ununited fractures of the neck of the femur without its being necessary to apply a plaster cast or use other methods of external immobilization. Judged by clinical as well as experimental test, the use of threaded steel wire is as satisfactory a method for the internal fixation of fractures of the intracapsular neck of the femur as other methods which have been described or observed.

The small threaded wire technic will continue as our method of choice because it is mechanically efficient and because we believe it to be physiologic, relatively atraumatic and less likely to contribute to delayed aseptic necrosis than methods requiring grosser trauma and greater displacement of cancellous bone of the fracture fragments.

Small threaded nuts on each wire may be tightened securely against the lateral cortex of the femur. This has been observed to increase the efficiency of the immobilization.

ABSTRACT OF DISCUSSION

DR. HAROLD R. BOHLMAN, Baltimore (presenting oral discussion for Dr. Austin T. Moore, Columbia, S. C.): Dr. Moore has treated 197 fractures of the hip, 70 per cent of which have been intracapsular, with no observation of nonunion since 1937.

He wishes to stress the following points: first, the necessity for perfect reduction; second, the need for impaction; third, the absolute necessity for rigid fixation, and fourth, drilling of the neck through the fracture site to reestablish circulation and facilitate healing.

He has enunciated the principle of four pins and feels that the fourth pin adds more than 25 per cent strength when the pins are properly placed. His principle of placing the pins parallel but spaced about the periphery of the neck is a point which he wishes to bring out emphatically. In this I agree with him from my experiments with the modulus of torsion in various types of internal fixation. The four pins when properly spaced about the periphery of the neck prevent eccentric movement and sheering stresses, which are great factors in producing nonunion of the neck of the femur by breaking down capillary bridging and thus starting the process of absorption of the neck.

Dr. Moore has checked the breaking forces and states that his figures are similar to those of Dr. Compere and associates.

The threaded wires of Dr. Compere give a great deal of fixation because there is a greater bearing surface and because when placed more transversely, they take care of the distraction force at the top of the neck or the area of tension. For this reason they may be placed more transversely than the rigid pins. The rigid pins have to depend on an oblique or an acute angle, because any further impaction

of the head or absorption in the line of fracture allows the proximal portion of the neck and the head to slide down on the pins.

Dr. Moore is thoroughly in accord with the feeling that pins and wires impact less bone than do flanged nails or larger appliances. Whatever the appliance, sheering stresses must be avoided. Wires and pins can be more easily removed and reinserted than flanged nails when readjustment is necessary.

DR. RUDOLPH S. REICH, Cleveland: Since the advent of the flanged Smith-Petersen nail I have used it in cases of fracture of the hip in which internal fixation was indicated. This method has superseded for me the many pins, screws and nails which were previously recommended, and my results have been much more satisfactory.

I was particularly struck by the comments Dr. Compere made regarding the occurrence of aseptic necrosis after the use of the Smith-Petersen nail. Since there are no exact statistics, it cannot be postulated that this occurrence is due to the use of the three-flanged nail. It may be due to the fact that the percentage of good results is larger since the introduction of the Smith-Petersen nail. Nevertheless, the occurrence of aseptic necrosis has concerned me considerably. Whether it is due to real damage to the circulation of the neck or the head of the femur cannot be determined. In my experience there have been cases in which aseptic necrosis in intracapsular fractures of the hip healed without any internal fixation.

I have a question I wish Dr. Compere would answer for me: Is the force that he exerted on these necks of femurs analogous to the force that is exerted when the hip is fractured? I wonder whether the force he used is not more a torsional than a distracting force.

I have not used Dr. Compere's threaded nails so I cannot report the results of any such experience. I should be interested to know what the end results will be. If the incidence of aseptic necrosis is reduced, I shall be happy to be converted from the three-flanged Smith-Petersen nail to the threaded nail of Dr. Compere.

DR. EDWARD L. COMPERE, Chicago: I am aware that the force which was exerted to produce these experimental fractures and repeated to test the breakdown strength or the holding power of the threaded wires or nails is not identical to that which clinically produces fractures of this type. I was primarily interested in testing the holding power of the wires, and believe that this was adequately demonstrated.

Although this method of internal fixation may decrease the incidence of aseptic necrosis, it will not prevent it entirely. The first patient treated by this technic has come into my office since this study was written. He complained of a little lameness in the hip. A roentgenogram revealed aseptic necrosis with the beginning of collapse of the head of the femur.

However, I do believe that it is justifiable to seek a method of internal fixation which is least likely to cause additional injury to the blood supply or to prevent revascularization.

I wish to emphasize that if a surgeon treats fracture of the hip, his responsibility and interest should extend beyond the mere healing of the fracture. He should be concerned about the blood supply to the head of the femur. He should not think of results in terms of immediate union of the fracture, but he should follow the patient for many years. Only in that way can he know exactly how effective any plan of treatment is. He should think of the end result in terms of the patient's ability to use the limb with strength, movement in the articulation and freedom from pain in the years to come.

ROLE OF ABDOMINAL DISTENTION IN LEUKOCYTE EXHAUSTION

JOHN VAN DUYN II, M.D.

SYRACUSE N. Y.

In a previous article¹ I reported 7 cases of leukocytic exhaustion characterized by leukopenia with a normal differential count and an extreme neutrophilic shift to the left. In 3 cases (cases 1, 2 and 3), the white cell failure followed either overwhelming or prolonged infection, but in the other 4 (cases 4, 5, 6 and 7) there was no such strain on the marrow to account for the blood picture. It was assumed, therefore, that in the latter group some impairment in leukopoietic power had been present all along, and these patients were considered to have a low leukocyte reserve. In 2 of the cases in which there was supposed low leukocyte reserve (cases 6 and 7), marked abdominal distention was present at the time of the lowest counts, and it was thought even at that time that some relation existed between the abdominal findings and the blood picture, though no explanation was offered as to its nature.

Since then 4 additional cases have been observed in which leukocytic exhaustion as defined appeared in the absence of severe infection and in the presence of marked abdominal distention. In case 2, hereinafter to be described, this association occurred on two separate occasions.

REPORT OF CASES

CASE 1.—H. C., a white man aged 30 years, was admitted to the Hospital of the Good Shepherd, Syracuse University, on Sept. 23, 1937, with symptoms of acute appendicitis of eighteen hours' duration.

The past history was not significant except for an attack at the age of 10 years of what was considered appendicitis.

Physical examination bore out the diagnosis of appendicitis in a well developed normal-appearing adult. No abdominal distention was present.

Table 1 shows that there was moderate preoperative leukocytosis with the expected differential picture. Preoperative urinalysis showed nothing abnormal.

At operation, performed shortly after admission, the appendix was removed in spite of its normal appearance, since no definite cause for the preoperative symptoms could be found. The pathologic report read: "Result of examination of appendix, negative."

On the morning after the operation abdominal distention was present and began to increase steadily. By September 26, the third postoperative day, distention was so marked that it required intestinal intubation with continual suction.

1. Van Duyn, J., II: Leukocytic Exhaustion Following Surgical Procedures, Arch. Surg. 37:302 (Aug.) 1938.

On September 27, a blood count was made which showed a low total white cell count with a marked neutrophilic shift to the left. On the following day injections of 6 cc. of concentrated extract of liver were started and continued for three days; in all, eight injections were given. The white cell count increased somewhat during this time, but the shift to the left continued extreme (table 1).

Throughout this period of marked distention, beginning on September 27, the urine showed increased concentration, persistent albumin (2 to 3 plus) and numerous casts of all types. The twenty-four hour output was reduced, ranging from 380 to 745 cc. during the four days beginning September 26.

The temperature rose gradually from an initial level of 100 F. to a range of 102 to 103 F. by September 30.

A roentgen plate of the abdomen taken on September 27 showed distention of the small intestine, cecum and ascending colon.

By September 30, seven days after the appendectomy, no improvement had taken place, and exploratory laparotomy was advised. At this operation the small

TABLE 1.—*Leukocyte Counts of the Patient in Case 1*

Date	White Blood Cell Count	Neutro- phils, per Cent	Lympho- cytes, per Cent	Mono- cytes, per Cent	Eosino- phils, per Cent	Nonfila- mented Neutro- phils, per Cent	Comment
9/23	10,000	83	14	3	0	Under 25	Before first operation
9/26	Marked distention
9/27	5,000	66	22	7	3	96	Basophils, 2 per cent
9/28 a.m.	5,400	55	39	6	0	96	Injections of extract of liver started
p.m.	5,300	67	23	5	5	95	
9/29 a.m.	7,700	70	18	12	0	97	
p.m.	10,000	70	19	10	1	96	
9/30 a.m.	10,500	55	30	13	2	92	Before second operation
p.m.	5,700	57	22	21	0	92	
10/1 a.m.	12,500	70	20	10	0	86	Blood transfusion
p.m.	14,200	70	25	5	0	77	

intestine was found markedly distended, and the colon, moderately so. There was no evidence of peritonitis. After operation the temperature rose sharply to 106.8 F. The course continued rapidly downhill, and the patient died on the following day. Necropsy was not performed.

CASE 2.—First Admission: C. L., a white woman aged 38 years, was admitted to the Hospital of the Good Shepherd, Syracuse University, on June 13, 1937, with a typical history of acute appendicitis of forty-eight hours' duration.

The past history revealed nothing unusual; the patient had always been healthy and active.

Physical examination confirmed the diagnosis of appendicitis but revealed nothing else significant.

The preoperative white blood cell count showed leukocytosis and an increase in the percentage of neutrophils as expected (table 2).

At operation, performed immediately, a gangrenous but unruptured appendix was removed, and the peritoneal cavity was drained. The pathologic report read: "Acute appendicitis."

The postoperative course was uneventful until the third day, when some abdominal distention developed. On June 18, two days later, the distention had become marked, and vomiting began. Aspiration of the contents of the stomach

was performed, and by the next morning the abdomen was soft. From this time on recovery was rapid and uneventful, and the patient was discharged on June 24.

The temperature never exceeded 101 F. after the third postoperative day. From a study of the urinary output no evidence of renal insufficiency was noted even during the period of distention.

Table 2 shows a sudden drop in the white cells together with a marked rise in the percentage of nonfilamented neutrophils on June 19, the fifth postoperative day, when the distention was first beginning to subside. The final count, made on June 21, two days later, showed a return of leukocytosis and a shift of the neutrophils back to the right. On this same day the patient began to menstruate.

Concentrated extract of liver was injected in doses of 3 cc. on three consecutive days beginning June 16 (table 2). It was started three days before the leukocyte drop was first noted.

Second Admission: On November 29, five months after appendectomy, C. L. was readmitted complaining of severe abdominal pain of twelve hours' duration with nausea.

TABLE 2.—*Leukocyte Counts of the Patient in Case 2, First Admission*

Date	White Blood Cell Count	Neutro- phils, per Cent	Lympho- cytes, per Cent	Mono- cytes, per Cent	Eosino- phils, per Cent	Nonfila- mented Neutro- phils, per Cent	Comment
6/12	24,000	89	17	3	0	..	Preoperative count
6/15	17,000	91	9	0	0	63	
6/16	18,500	93	6	1	0	53	Injectons of extract of liver started
6/17	12,500	84	12	2	1	55	
6/18	Distention at height
6/19	7,200	63	29	2	1	86	
6/21	14,500	73	25	0	2	66	Menstruation

Physical examination showed evidence of intestinal obstruction, and laparotomy was performed five hours after admission.

At operation a volvulus of the lower part of the ileum was found; there was gangrene in the portion caught in the loop. The gangrenous 2 feet (61 cm.) of ileum was resected; enteroenterostomy was performed, and the wound was closed without drainage.

The next morning there was moderate generalized abdominal distention, and small emeses were frequent. The stomach had to be aspirated repeatedly, as the patient would not permit continual suction. On December 2, three days after operation, the distention began to decrease and by the fourth day had completely subsided. From this time on, progress was uneventful, and the patient was discharged on December 11.

The temperature on admission was 99 F. On the first day after operation it rose to 101.4 F. but never again exceeded 100.6 F. Urinalysis and study of the urinary output revealed no evidence of renal insufficiency either before or after operation.

The two preoperative white blood cell counts were made four hours apart; both showed the expected marked leukocytosis and appropriate differential counts, including the moderate shift to the left of the neutrophils (table 3). Postoperatively, however, there was a sharp drop in the total count together with a marked increase in the percentage of nonfilamented neutrophils associated with the abdominal dis-

tention. On this occasion also the blood picture returned to normal along with the subsidence of the abdominal symptoms and the onset of menstruation.

Injections of extract of liver had again been given prophylactically (table 3) and in the same doses as before.

CASE 3.—I. A., a white woman aged 50 years, was admitted to the Hospital of the Good Shepherd, Syracuse University, on Sept. 11, 1938, complaining of severe abdominal pain of three days' duration.

The past history showed diabetes over a period of nineteen years under good control with small doses of insulin. From 1932 on, there were recurring attacks of gallstone colic until cholecystectomy was performed on Jan. 18, 1936. Two months after the operation, while the patient was still in the hospital, intestinal obstruction developed. At operation, the cecum was found markedly distended owing to a volvulus with adhesions. The obstruction was relieved, and cecostomy was performed with subsequent recovery. Five months later, the patient was readmitted

TABLE 3.—*Leukocyte Counts of the Patient in Case 2, Second Admission*

Date	White Blood Cell Count	Neutro- phils, per Cent	Lympho- cytes, per Cent	Mono- cytes, per Cent	Eosino- phils, per Cent	Nonfila- mented Neutro- phils, per Cent	Comment
11/29	21,000	96	3	1	0	38	Preoperative count, 11:30 a.m.
	31,000	93	3	4	0	51	Preoperative count, 3:30 p.m.
11/30	Injections of extract of liver started
12/ 1	6,700	59	39	1	1	92	Distention at height
12/ 2	7,600	71	29	0	0	77	Menstruation
12/ 3	8,000	66	25	7	1	77	Basophils, 1 per cent
12/ 7	15,400	54	45	1	0	50	

with recurrence of the obstruction, but on this occasion relief followed intubation without surgical intervention.

A third attack of obstruction began suddenly three nights before admission with severe generalized abdominal pain, increasing distention and obstipation. Vomiting began on the morning of admission.

Physical examination revealed an elderly woman in severe pain. The temperature was 99.2 F.; the pulse rate, 90, and the respiration rate, 20. There was marked abdominal distention with generalized tenderness, a large umbilical hernia, and an old scar over the right rectus muscle.

The preoperative leukocyte count was: white blood cells, 3,300; neutrophils, 34 per cent; lymphocytes, 53 per cent; monocytes, 12 per cent; eosinophils, 1 per cent; 94 per cent of the neutrophils were nonfilamented. Preoperative urinalysis revealed no abnormalities, except that many red and white cells were visible microscopically.

At operation, performed several hours after admission, the ascending and transverse portions of the colon were enormously distended from the terminal part of the ileum to the splenic flexure owing to a *volvulus of this entire length of bowel*. No evidence of infection was present. During the untwisting of the volvulus the ileum was torn, and the fecal contents were spilled. The tear was repaired and enterostomy done.

After operation the patient fared poorly and died on the third day.

Necropsy showed acute peritonitis, acute pericarditis, bilateral hydrothorax and acute and chronic pyelonephritis with some hydronephrosis. There was also perihepatitis, periportal infiltration and some fatty degeneration of the liver.

CASE 4.—A. T., a white man aged 77 years, was admitted to the Syracuse Memorial Hospital on May 31, 1939, complaining of pain in the back on the right side radiating through to the right upper quadrant of the abdomen. This pain had been occurring for one year and had increased in frequency and severity during the previous six weeks.

The past history showed that ten years previously cholecystectomy and appendectomy had been performed but that neither stones nor inflammation of the gallbladder had been found. There had never been jaundice to the patient's knowledge. There was also a history of peptic ulcer with two hospitalizations, nine and seven years before, respectively.

Physical examination revealed an elderly, well preserved man, not acutely ill. The temperature, the pulse rate and the respiration rate were normal. There was a questionable subicteric tint to the scleras, but aside from this and the old abdominal scars, there were no positive findings.

TABLE 4.—*Results of the Examination of the Blood of the Patient in Case 4*

Date	White Blood Cell Count	Neutro- phils, per Cent	Lympho- cytes and Mono- cytes, per Cent	Eosino- phils, per Cent	Nonfla- mented Neutro- phils, per Cent	Non- protein Nitrogen, Mg. per 100 Cc.	Comment
6/ 1	5,700	60	31	9	Under 25	32	Admission
6/ 6	Operation
6/ 8	Distention begun
6/ 9	109	
6/10	5,700	80	20	0	95	..	Distention at height
6/13	15,000	80	16	4	40	139	Distention subsided
6/22	10,200	74	23	3	27	38	

The preoperative blood count was not unusual except for eosinophilia, the significance of which is not clear (table 4). Examination showed that the urine and the nonprotein nitrogen were normal. The icteric index was 8, and the van den Bergh test had a slight positive indirect reaction.

At operation, performed on June 6, adhesions were noted about the common duct and were freed. No other cause for the symptoms was discovered.

On June 8, the second day after operation, there was some abdominal distention, and two days later this had become marked in spite of the usual decompression procedures. However, on June 11, the distention began to subside and was gone in forty-eight more hours.

During the period of distention there was present not only failure of the usual postoperative leukocytosis and an extreme neutrophilic shift to the left but also marked renal insufficiency, as shown by the high figures for nonprotein nitrogen in the blood (table 4). The urinary output also was significantly diminished, averaging some 300 cc. in twenty-four hours from June 7 through June 10.

The temperature was elevated to a maximum of 102 F. on June 10 and June 11 but returned to normal rapidly thereafter together with the blood picture and, though more slowly, the nonprotein nitrogen.

The patient was discharged on July 20 as improved, and, up to October 1940, when last followed, had continued at work.

COMMENT

In all 4 cases, including the five admissions, a picture of leukocytic exhaustion coincided with marked abdominal distention in the absence of severe infection. Although blood counts were insufficient to prove that the distention always preceded the white cell failure, yet at least in no instance was the significant blood picture found before the distention had reached its height.

In cases 1, 2 (both admissions) and 4, the distention was of the postoperative paralytic type; in case 3, it was mechanical.

In cases 1 and 4, renal insufficiency was associated with the abdominal distention and white cell failure. In cases 2 and 3, however, this was not observed.

Injections of concentrated extract of liver were followed by some elevation of the white blood cell count in case 1, but in neither admission in case 2 did prophylactic injections prevent the exhaustion picture from developing.

In case 2, the onset of menstruation coincided with the subsiding of the abdominal distention and the return of the blood picture to normal in both admissions. This may not be entirely coincidental, but the significance is not clear and will not be discussed.

Of these 4 reported cases only in cases 3 and possibly 4, might it be assumed that a low leukocyte reserve was present all along. In cases 1 and 2 the patients were vigorous young adults with essentially noncontributory past histories.

SIGNIFICANCE OF THE DEGENERATIVE BLOOD PICTURE

The most important question to be answered from these cases is: Since severe infection did not bring about the picture of white blood cell failure, can abdominal distention have been responsible?

Before taking up this question, however, another will be considered: Does the blood picture in the 4 cases reported confirm or contradict the apparent absence of infection?

To answer this, blood smears in 3 of the 4 cases reported here (the blood smears in case 4 were not available) and in 2 similar cases previously reported (cases 6 and 7)¹ were reviewed. The smears selected were those made in each case at the time of the lowest count and the highest nonfilamented neutrophil percentage (table 5, series 1).

These blood counts were compared with those from a second series of cases in which there was similar leukocytic exhaustion (table 5, series 2). In the latter, however, distention, though present, was less marked on the whole, and severe infection was present in an apparently sufficient degree to have overwhelmed the marrow.

The degree of infection or other irritation of the marrow in each case is indicated in table 5 under "Strain on the Marrow." Three hundred cells were counted in each instance, except in smear 10, in which only 200 cells were counted. The usual Schilling differential blood count was made, except that juvenile cells were not separated from the stubs owing to the difficulty in many instances of satisfactorily differentiating them. Under "Myelocytes" both early and late forms are included. Although myelocytes are reported under their own heading, they are included in the neutrophil percentages besides. A few

TABLE 5.—*Comparison of Two Series of Leukocyte Counts*

Smear	Age of Patient, Years	Sex of Patient	Series 1. Marked Distention; No Severe Infection								Strain on the Marrow
			White Blood Cell Count	Neutrophils, per Cent	Myelocytes, per Cent	Lymphocytes, per Cent	Monocytes, per Cent	Eosinophils, per Cent	Basophils, per Cent	Nonfilamented Neutrophils, per Cent	
1 (case 6 ¹)	3,200	60.7	0	21.0	17.0	0.7	0.7	93	Laparotomy and salpingitis Parturition Appendectomy Appendectomy
2 (case 7 ¹)	3,500	66.0	0	20.0	13.3	0.7	0	93	
3 (case 1)	5,400	65.7	0	19.0	12.3	2.3	0	95	
4 (case 2, first admission)	7,200	64.3	0	22.3	12.3	1.0	0	93	
5 (case 2, second admission)	6,700	55.3	0	30.3	9.3	2.0	0	91	Intestinal resection
6 (case 3)	3,300	34.3	0	53.0	11.7	1.0	0	94	Preoperative volvulus
Series 2. Severe Infection; More or Less Distention											
7.....	67	M	3,600	74.3	5.7	18.3	7.0	0	0.3	98	General peritonitis and carcinoma General peritonitis
8.....	23	F	3,000	91.0	2.3	7.0	2.0	0	0	93	
9.....	75	M	7,000	70.0	4.0	26.3	3.7	0	0	95	General peritonitis
10.....	63	M	2,400	47.0	4.5	52.5	0	0	0.5	98	Lobar pneumonia
11.....	7	M	8,800	82.7	2.3	17.3	0	0	0	95	Bronchopneumonia

unclassified cells and a rare blast form or two were encountered but disregarded. The nonfilamented neutrophil counts are reported in all tables in percentages related to the total of neutrophils and not to the total of cells.

The counts in table 5 were all made by me; they were all made from cover slip preparations except smears 1 and 10, which were made from slide films.

Comparison of the two series of cases in table 5 shows the following differences: As to neutrophils, in series 1 there was a complete lack of neutrophilia (no case with neutrophils over 66 per cent), and there was even actual neutropenia (neutrophils, 34.3 per cent in smear 6); in series 2 there was a wide spread in the neutrophil percentages, the

variations ranging from neutrophilia (neutrophils 91 per cent in smear 8) to neutropenia (neutrophils 47 per cent in smear 10).

The nonfilamented neutrophil count was extremely high in both series, being 93 per cent or more in every instance. Toxic granules (not listed) were found in almost 100 per cent of the neutrophils of both series.

Myelocytes were uniformly absent in series 1 but uniformly present in series 2.

The percentages of lymphocytes did not appear to be distinctive in either series but ranged somewhat higher in series 1, following the lower neutrophil percentages.

The monocyte percentages in series 1 were increased, ranging from 9.3 to 17 per cent. In series 2, they were decreased, ranging from 0 to 7 per cent.

Eosinophils in series 1 were uniformly present; in series 2, uniformly absent.

Thus in series 1 the absence of neutrophilia and myelocytes and the presence of monocytosis and eosinophils confirmed the clinical absence of severe infection; in series 2, the almost uniformly opposite findings, especially with regard to myelocytes, monocytes and eosinophils, confirmed the presence of infection.

Low total white blood cell counts with marked neutrophilic shift to the left were found in both series (table 5). In the cases of series 1, this would seem to contradict the indications of the other blood findings with regard to the absence of any severe infection, since leukopenia and high percentages of nonfilamented neutrophils are usually thought of as associated with marrow failing from overwhelming irritation. Schilling,² however, has shown that the shift to the left and the falling total count are not always due to collapse of the hemopoietic cells from overwork but may be the result of a "degenerative inhibition of development." The ordinary neutrophilic shift to the left, due to simple stimulation (as in pyogenic infections) with the eventual output of juvenile cells and myelocytes as the stimulus increases, he called regenerative; the other type of shift to the left, which is due to actual inhibition in development resulting in the output of stab neutrophils without young forms, he called degenerative. The regenerative and the degenerative neutrophilic shift are thus qualitatively distinct and not merely the results of different degrees of the same stimulation.

With the regenerative shift, leukocytosis is the rule; with the degenerative shift, decrease in total counts to the point of leukopenia

2. Schilling, V.: *The Blood Picture and Its Clinical Significance*, St. Louis, C. V. Mosby Company, 1929, pp. 146-154 and 244.

occurs. It seems generally accepted that a decreasing total count may also accompany a regenerative shift in the presence of continued severe infection as the result of overstimulation with exhaustion of the marrow. In what number of these instances, however, the leukocyte drop is in reality due to a degenerative influence cannot be estimated as yet.

Moderate and even marked degrees of neutrophilic shift to the left may result from stimulation alone (regenerative shift), but when the shift is extreme, with over 80 and even 90 per cent of the neutrophils nonfilamented, this is undoubtedly due to the inhibitory influence (degenerative shift).

Naegeli³ also recognized the degenerative stab, pointing out that "toxic influences may interrupt the maturation of the cells [the neutrophils] and cause such changes in their structure as to prevent any accurate estimation of their age by Arneht's method." For this reason I have preferred to use the expression "shift to the left" rather than "immature" in speaking of the neutrophilic stab. "Shift to the left" means no more than it says, while "immature" as a description of the degenerative stab appears to tell only part of the story.

The low counts and the extreme shifts to the left in series 1 (table 5) represent degenerative qualities, then, and do not contradict the evidence of the rest of the count that no severe infection is present. Moreover, the occurrence of these same qualities in series 2 (table 5) indicates that a degenerative influence exists along with the regenerative, i. e., that in these cases there is a mixed degenerative-regenerative picture.

Schilling² did not state in so many words that the degenerative blood picture could occur in the total absence of infection or even that it could exist in a pure form, i. e., without regenerative elements. In his remarks on prognosis, however, he does describe a blood picture similar to those in the cases in series 1 (table 5) in which the prognosis is "not unfavorable" and in which no regenerative elements are present. His words are as follows: "Subnormal counts with degenerative shift of the neutrophils, lymphocytosis, monocytosis and presence of eosinophils per se are not unfavorable." Of the 5 patients in series 1 (pure degenerative picture) only 2 died; of the 5 in series 2 (mixed degenerative-regenerative picture) all died.

Thus the answer to the question of whether or not the blood picture in the 4 cases reported actually confirmed the clinical absence of severe infection is in the affirmative.

3. Naegeli, K., cited by Musser, J. H., and Wintrobe, M. W., in Tice, F.: *Practice of Medicine*, Hagerstown, Md., W. F. Prior Company, Inc., 1921, vol. 6, p. 739.

ROLE OF ABDOMINAL DISTENTION IN THE PRODUCTION OF THE
DEGENERATIVE BLOOD PICTURE

I shall return now to the first question, which was in substance: Can the distended intestine in the 4 cases reported here and in the 2 previously reported (cases 6 and 7)¹ have been the cause of the associated degenerative blood picture?

In these 6 cases (comprising 7 admissions), abdominal distention was of the postoperative paralytic type in all but 1, and the involvement apparently included the colon in every instance. Accordingly, a further study of the blood picture occurring with distention was directed toward mechanical obstructions and those occurring at or above the level of the ileocecal valve. Recent cases of this type were reviewed from the records of the Hospital of the Good Shepherd, Syracuse University, and the Syracuse Memorial Hospital. Other criteria of selection were the presence of abdominal distention, complete obstruction as proved by operation, adequate preoperative blood counts and the absence of complicating factors, such as infection and gangrene, at the time of the counts.

The first 20 cases in which these requirements were fulfilled were used. The causes of the obstruction were: adhesions in 12 cases; intussusception in 3 cases; hernia in 2 cases, and volvulus, Meckel's diverticulum and gastroenterostomy, each in 1 case. The levels of obstruction varied as follows: the jejunum in 2 cases; the upper part of the ileum, 2 cases; the lower part of the ileum in 11 cases; and the terminal part of the ileum in 5 cases. The obstructions had been present for periods of one-half day to five days before hospitalization; i. e., before the first blood count.

In 5 of the 20 cases the blood picture showed unmistakably degenerative tendencies. (In the other 15, these tendencies were not apparent.) In 4 of the 5, the total white blood cell count was low, and the shift to the left was marked. In the fifth, in which two preoperative counts were reported, the degenerative tendency was evidenced by the increased shift to the left and the decreased percentages of neutrophils in the second count as compared with the first, though the original leukocytosis persisted.

The duration and the level of the obstruction may be important factors in determining the onset of the degenerative changes, though in my small series this cannot be demonstrated. Such a possibility is apparently considered by Demidova,⁴ who found in a study of the white blood cell count in cases of acute ileus that in the group in which "toxic"

4. Demidova, P. N.: Blood Picture in Acute Ileus, *Vestnik khir.* 56:356 (Sept.-Oct.) 1938; abstracted, *J. A. M. A.* 112:1775 (April 29) 1939.

obstruction was noted of the small intestine leukocytosis was soon replaced by leukopenia.

Thus the degenerative blood picture may occur with distention of the small as well as with distention of the large intestine and with mechanical obstruction as well as with paralysis, and still without evidence of any complicating infection or necrosis.

These findings go still farther in confirming abdominal distention itself as the cause of degenerative changes in the blood picture. The actual mechanism must be in the inhibiting of the hemopoietic function of the marrow by some toxic substance, apparently nonbacterial in origin and possibly absorbed from the distended intestine. The effect of the hypothetic substance on leukopoiesis is purely inhibitory and not due to overstimulation such as is supposed to occur at times from overwhelming infection.

TABLE 6.—*Leukocyte Counts of Patients with Uncomplicated Mechanical Abdominal Obstruction*

Pa- tient	Sex	Age, Yr.	White Blood Cell Count	Neu- tro- phils, per Cent	Lym- pho- cytes, per Cent	Mono- cytes, per Cent	Eosino- phils, per Cent	Nonfla- mented Neu- tro- phils, per Cent	Dura- tion of Ob- struc- tion, Days	Level of Obstruction
1	M	58	5,200	55	37	8	0	87	4	Lower part of ileum
2	F	49	5,700	81	16	3	0	86	2	Terminal part of ileum
3	F	60	6,600	51	45	4	0	64	5	Lower part of ileum
4	M	60	7,300	83	—16—		1	55	3	Upper part of ileum
5	M	22	21,000 18,000	94 44	4 44	2 11	0 1	42 88	1 2	Lower part of ileum

But what of abdominal distention that is secondary to pyogenic infection? Can degenerative influences also develop from this, and if so, can they be distinguished from the regenerative influences originally present?

Illustrations of this situation are found in the 5 cases of series 2 (table 5). In the first 3 cases there was general peritonitis; in the last 2, bilateral pneumonia. The blood pictures were all of the mixed degenerative-regenerative type already mentioned and both degenerative and regenerative influences could be distinguished. The regenerative elements consisted of neutrophilia (when present), presence of myelocytes and lack of eosinophils; the degenerative, of low total white blood cell count, normal neutrophil percentage or actual neutropenia (when present) and extremeness of the neutrophilic shift to the left. Even though pyogenic infection was the primary disorder in these 5 mixed cases, the degenerative elements might well have been the result of secondarily developing abdominal distention and not of overwhelming of the marrow.

The consideration of abdominal distention as at least a contributing cause of white blood cell failure in cases of pneumonia is of especial interest and deserves more discussion than can be given here. It may be said, however, that whenever the degenerative tendency appears with pneumonia (as, for that matter, with any infection, whether intra-abdominal or extra-abdominal), associated paralytic intestinal distention should always be looked for.

DEGENERATIVE BLOOD PICTURE OF GASTROINTESTINAL TRACT INVOLVEMENT OTHER THAN ABDOMINAL DISTENTION

There is one other type of condition showing the degenerative blood picture that deserves consideration here. This is the condition in which the gastrointestinal tract is diseased but in which abdominal distention is not an outstanding characteristic. Examples of this are typhoid (as is well known),² certain epidemic forms of bacillary dysentery⁵ and, frequently idiopathic ulcerative colitis.⁶ With all these conditions the degenerative characteristics of the blood picture are striking. Although abdominal distention may not be clinically present, it is not difficult to imagine that in these instances in some way the same toxic absorption is taking place as in cases in which distention is actually demonstrable. However, whether the absorption is due to a subclinical distention or to the involvement of the intestinal wall by bacteria or ulceration is not known.

It is altogether possible, of course, that the inhibiting substance is formed indirectly by some intermediate organ as, for example, the liver. The sequence of events would then be: (1) absorption of toxic products from the wall of the intestine (either distended or involved in some other way); (2) damage to the liver by the toxins with disturbance of liver function, and (3) production of a second toxic substance, the actual leukopoiesis-inhibiting one, by the damaged liver. Theoretically, then, the liver might under certain conditions be capable of forming the inhibiting substance directly, i. e., in the absence of any gastrointestinal disease whatever.

5. Ginsburg, H. M.; Hirschberg, E. M., and Brisker, F.: Bacillary Dysentery: A Preliminary Report Stressing the Blood Picture, *J. A. M. A.* **113**:1321 (Sept. 30) 1939.

6. Moltke, O.: Number and Percental Apportionment of White Blood Corpuscles in Suppurative Coloproctitis, *Bibliot. f. læger* **128**:83 (April) 1936; abstracted, *J. A. M. A.* **107**:172 (July 11) 1936. Garvin, R. O., and Bagen, J. A.: The Hematologic Picture in Chronic Ulcerative Colitis: Its Relation to Prognosis and Treatment, *Am. J. M. Sc.* **193**:744 (June) 1937. Vickers, P. M., and Bagen, J. A.: An Index of Prognosis in Thrombo-Ulcerative Colitis, *Proc. Staff Meet., Mayo Clin.* **13**:408 (June 29) 1938.

It should be understood that I am not attempting to show that all types of leukopenia are due to the inhibiting action of some hypothetic toxic substance. Obviously, those of agranulocytosis, aleukemic leukemia and aplastic anemia are of fundamentally different natures from that of the degenerative blood picture. I have sought only to bring out that at least one type of leukopenia, the one characterized by the degenerative shift, appears to be the result in certain instances of intestinal distention. Perhaps, however, the origin of degenerative leukopenia in many other conditions, such as influenza, kala-azar and pappataci fever,² will eventually be found explainable on the basis of the same hypothesis as to the formation of the inhibiting substance.

Kaufman and vom Saal⁷ recently published an article on the white blood cell counts of patients with various intra-abdominal diseases. They found that a marked neutrophilic shift to the left may occur "in all types of acute peritoneal irritation, even without infection." This depends on "sudden peritoneal shock or irritation" and is "probably due to inflammation of a chemical nature."

Whatever may ultimately prove to be the cause of the degenerative blood picture, whether abdominal distention, peritoneal irritation or some other factor, the observation of Kaufman and vom Saal that a marked neutrophilic shift to the left may occur even without infection is of great importance and is fully confirmed by my observations. It means, for instance, that an abnormally high or increasing nonfilamented neutrophil count is no longer to be taken as an inevitable indication of the onset, the spread or even the presence of infection. Such a count may, for example, be merely the result of temporary postoperative distention.

A study of the white blood cell picture in cases of leukocytic exhaustion with regard to its degenerative and regenerative qualities, then, may be of great value to the surgeon since the question as to the presence or absence of infection in a given case, which may sometimes be vital, may also at times be answerable by this procedure.

SUMMARY AND CONCLUSIONS

Four cases are reported and 2 cited from a previous article; all illustrate the association of leukocytic exhaustion with abdominal distention in the absence of severe infection. The blood picture in these cases in which there is no severe infection is compared with cases showing a similar white blood cell failure, but in which severe infection is present. In the former the blood picture is purely degenerative; in the latter, mixed degenerative-regenerative.

7. Kaufman, R. E., and vom Saal, F.: Leukocyte Changes in Acute Peritoneal Irritation, *J. Lab. & Clin. Med.* **26**:468 (Dec.) 1940.

The pure degenerative blood picture is characterized by: low to leukopenic white blood cell counts, normal to neutropenic neutrophil percentages, absence of myelocytes, normal to increased percentages of lymphocytes and monocytes and presence of eosinophils. In the mixed degenerative-regenerative picture, regenerative elements are found, such as neutrophilia, presence of myelocytes, monocytopenia and absence of eosinophils.

The prognosis in cases of leukocytic exhaustion with pure degenerative shift is "not unfavorable" (Schilling²); however, with mixed degenerative-regenerative shift the condition is fatal.

In a series of cases of uncomplicated mechanical obstruction of the small intestine with distention, in 5 out of 20 the degenerative tendency was present. In 5 cases of peritonitis and pneumonia in which there was leukocytic exhaustion with mixed degenerative-regenerative shift, the degenerative elements were distinguishable from the regenerative. Abdominal distention was present in all 5 cases.

The degenerative type of white blood cell failure may also be found with disease of the gastrointestinal tract other than that associated with obvious abdominal distention. Examples of this type of disease are typhoid and certain types of dysentery and colitis.

Abdominal distention is concluded to be at least one important cause of the degenerative blood picture. The actual mechanism of production is through absorption from the distended intestinal wall of some apparently nonbacterial toxic substance which acts either directly or indirectly as an inhibitor of leukopoiesis.

Thus, a low or falling white blood cell count with marked neutrophilic shift to the left and toxic granulations does not necessarily mean that the marrow is overwhelmed by infection, that the patient's resistance is abnormally low or that the prognosis is bad; it may be due to a purely degenerative influence.

A fuller study of the white blood cell picture is urged in all cases of leukocytic exhaustion, particularly if the question as to the presence or absence of infection is important.

Drs. E. S. Van Duyn and T. L. Bryant's cases are reported with their permission; blood smears were lent by Dr. E. G. Allen; the staffs of the library of the Syracuse University College of Medicine and the record rooms of the Hospital of the Good Shepherd, Syracuse University, and the Syracuse Memorial Hospital cooperated in the preparation of this study.

713 East Genesee Street.

INCIDENCE OF MALIGNANT GROWTH OF THE UNDESCENDED TESTICLE

A CRITICAL AND STATISTICAL STUDY

HORACE E. CAMPBELL, M.D.*

DENVER

Whether the undescended testicle is more liable to become the seat of malignant change than the scrotal testicle and whether, of undescended testicles, the inguinal is more likely to be affected than the abdominal are two questions which have not been satisfactorily answered. In 1927 Wangenstein wrote, "No greater diversity of opinion probably exists concerning anything in medicine than the question of malignancy in the undescended testis." In 1936 Hinman said, "Whether tumor is relatively more frequent with inguinal than with abdominal retention is uncertain."

From the data recorded in the literature it can now be stated unequivocally that the undescended testicle is more liable to malignant change than the normally placed testicle and that the abdominal testicle is more liable to malignant change than the inguinal.

There are at least six main reasons why these truths have so long remained obscure: 1. The medical profession has neglected the science of statistics; it has tried to draw conclusions from figures without knowing how to manage them. 2. Medical authors have committed almost incredible errors of misquotation. 3. Differing definitions of the words "cryptorchidism," "cryptorchid," "ectopy," "anorchidism" and "monorchidism" have led several authors to false conclusions. 4. Authors have tended to publish statistics from their hospital practice and to neglect the implication of the figures from their private practice. 5. During the early years of discussion of malignant growth in the undescended testicle, preceding and following Johnson's first recorded case of malignant growth in the abdominal testicle in 1859, the number of reported cases of malignant growth in the inguinal testicle greatly exceeded that of cases of malignant change in the abdominal testicle. That disproportion no longer exists, probably because the abdomen is

* Research Fellow in Surgery of the Harvard Medical School and George Gorham Peters Traveling Fellow in Surgery of the Peter Bent Brigham Hospital.

From the Laboratory for Surgical Research of the Harvard Medical School and the Surgical Service of the Peter Bent Brigham Hospital, Boston.

much more frequently explored than in those years. Yet those early figures are still extensively quoted and continue to create an erroneous impression. 6. The incidence of malignant change in the undescended testicle has been computed in terms of the number of patients. If the incidence is computed in terms of the number of testicles, the cases of malignant change in bilateral undescended testicle achieve their true significance.

STATISTICAL AND HISTORICAL REVIEW

The Science of Statistics.—Opinion concerning the probability of malignant change in the testicle has varied from decade to decade largely because physicians have not been aware of the theories of chance variation and have not tested their conclusions by criteria based soundly on the science of statistics. It is the duty of physicians who attempt to draw conclusions from statistics to become acquainted with the statistical method. Otherwise, erroneous conclusions will probably result. The writings of Fortuyn were instrumental in introducing me to the subject of statistics, and they still remain the simplest and shortest presentation. The writings of Hill in the *Lancet* have been published in book form and constitute the best approach for the busy practitioner. The articles were written for physicians and deserve widespread reading in America. It is to be hoped that eventually every medical student will be taught a working knowledge of the statistical method.

Not the least essential part of the statistical method is the assemblage of data. The data as recorded in the literature on the undescended testicle leave much to be desired. For example, there is the matter of the meaning of "hospital admissions." It is a fact that many patients are readmitted and hence in a table of "hospital admissions" are counted again and again. In one hospital it is estimated that 50 per cent of the total admissions are readmissions. In another hospital 1 patient was readmitted thirteen times in one year, and it was estimated that between 15 and 20 per cent of the total admissions were readmissions. If medical writers are to deal with figures, they must persuade hospital administrators to adopt a different system of recording than is now employed in most hospitals.

In this regard is the matter of sex. Many hospitals do not record the numbers of male and female patients. It is often assumed that about half are male and half female, but an active gynecologic service will cause this proportion to vary considerably. The sex incidence of disease does not greatly interest most writers, but in considering a subject of the sort dealt with here an accurate idea of the number of male patients observed becomes important.

One of the most disappointing features of this study was the large number of writers who did not tell the proportion of abdominal and of

inguinal testicles among undescended testicles in which there was no malignant growth. They give the number of patients with undescended testicle but give no indication of how many had bilateral nondescent or how many had nondescent of testicles in the various locations. While it has been possible to collect a sufficient number of papers giving these details to render conclusions drawn from them statistically sound, the task might have been much easier and the figures much larger if all the writers on the subject had given all the data.

Misquotations.—The subject of malignant growth in the testicle contains many inherent complexities; it is confusing without the complications of misquotation.

The most startling example of misquotation in recent years was the misinterpretation by Hinman, a recognized authority, of a statement by Coley, an outstanding authority of two decades ago. In 1915 Coley wrote:

. . . At the Hospital for Ruptured and Crippled, from 1890-1907, in 59,235 cases of inguinal hernia in the male sex there were found 737 cases of undescended testis, without a single case of sarcoma of the undescended testis.

In 1924 Hinman wrote:

. . . Coley, for instance, in 59,235 cases of inguinal hernia, in the Hospital for Ruptured and Crippled Children, from 1890-1907, encountered malignancy of the undescended testicle 737 times—1 in every 80—an unbelievably high incidence . . .

Less startling but more far reaching, for it has been widely repeated, is the following instance of misquotation. In 1913 Bulkley wrote:

. . . Thus in 182,729 male admissions to general hospitals, there were 3 cases of malignant growths of intra-abdominal testicles, or about 1 in each 60,000 cases.

In 1924 Hinman, basing his figures on those of Bulkley, said:

. . . About 1 in every 1500 male admissions has teratoma as compared to 1 malignant abdominal cryptorchid in every 60,000 admissions of cryptorchid . . .

This statement was used by MacKenzie and Ratner to fortify their thesis that the abdominal testicle undergoes malignant change less frequently than the inguinal.

A frequently quoted misquotation is that by Coley of a statement of Bulkley. In 1913 Bulkley wrote:

. . . My statistics from the Presbyterian Hospital show 2 cases of malignant abdominal and no cases of malignant inguinal testes.

In 1915 Coley wrote:

. . . Bulkley, himself, however, found at the Presbyterian Hospital 2 cases of malignant abdominal in 12 cases of malignant inguinal testes.

Perhaps the most widely circulated error of quotation occurred early in the literature on this subject. In 1869 Schaedel wrote, as his graduation thesis in medicine, "Ueber Kryptorchidie." In his remarks about malignant growth in the testicle he wrote:

. . . Während in den Jahren 1853-1859 in den grössten Londoner Spitälern 36 Carcinome normaler descendirter Hoden behandelt wurden, kamen in demselben Zeitraume in den nämlichen Spitälern 5 Carcinome retinirter Hoden zur Operation. (During the years 1853-1859, 36 carcinomas in normally descended testes were treated in the largest London hospitals; in the same period 5 carcinomas in retained testes came to operation in the same hospitals.)

In 1887 von Kahliden quoted Schaedel and mistakenly gave the period as 1853 to 1854. In practically every compilation of statistics since that time these figures have occurred, the series being attributed to von Kahliden more often than to Schaedel. Not long after, another writer, quoting this statement from von Kahliden (few give evidence of having consulted Schaedel in the original), interpreted the figures as coming from a large London hospital. In this doubly erroneous form the passage has been widely quoted, and much space has been used in repudiating the possibility that such a large number of cases could have come from any hospital in one year.

In a copy of Schaedel's dissertation obtained from the Library of Congress no reference was found for the aforementioned statement. Schaedel cited (with an incomplete reference) a case reported by Mr. Partridge. This case was 1 of 36 collected by the editors of the *Medical Times and Gazette* from the pages of that publication for the six years preceding the report in September 1859. These must be the 36 cases to which Schaedel referred. They were from eleven of the well known London hospitals together with nine of the provincial hospitals. No reference could be found for the 5 cases of carcinoma of the retained testis said by Schaedel to have come to operation during the same period. Only 2 cases of malignant growth in the undescended testicle could be found in the literature for the period 1853 to 1859, and in only 1 of these was operation performed. In Spry's case the patient was operated on and recovered. He wrote:

. . . It appears that the only two cases of excision of diseased testes, retained in the groin, performed in this country, are those recorded by Mr. Arnott, of the Middlesex Hospital (1845), and by Mr. Storks of Gower-street (1847).

In Johnson's case operation was not performed. At autopsy a malignant condition of the abdominal testicle was found. This is probably the first recorded case of malignant change in the abdominal testicle. In his book on diseases of the testis Curling wrote:

. . . There are many cases on record of carcinoma affecting testicles retained in the groin.

Later in the book he wrote :

. . . The excision of a testicle detained in the groin and affected with malignant disease has been performed by Arnott of the Middlesex Hospital (1845) and Storks of Gower-street (1847), Spry of Truro (1857) and Fayrer of Calcutta (1857).

Another editorial report of the *Medical Times and Gazette* lists 6 cases of cystic sarcoma of the testicle occurring during the same period, 3 in London and 3 in the provinces. In all 6 cases the involved testis was normally descended.

Definition of Terms.—Different definitions of "cryptorchidism" and related terms have been the source of much confusion and some actual error. Some consider "cryptorchidism" to mean bilateral abdominal retention; this might be the literal meaning. Most writers use the term to refer to any degree of incomplete descent in one or both testicles. This usage is in accord with Webster's "New International Dictionary of the English Language," in which "cryptorchidism" is defined as signifying "a condition in which the testes fail to descend normally"; and "cryptorchid," as signifying "one affected with cryptorchidism." Many physicians consider a cryptorchid to be an undescended testicle. According to Stedman's "A Practical Medical Dictionary," a cryptorchid is "one whose testes have not descended into the scrotum." The aforementioned dictionaries will be followed in the use of these terms. "Ectopy" is used by some as synonymous with "cryptorchidism"; by others it is used in relation to perineal, penile and femoral locations. It will be used in the latter sense, that is, as designating a type or subdivision of cryptorchidism.

Confusion likewise has arisen from the loose use of "monorchidism" and "anorchidism." The former should not be used to mean unilateral abdominal retention; nor should the latter be used for bilateral abdominal retention. The terms should be used as indicating that the patient actually has either one or no testicles, as the case may be. As congenital defects, monorchidism and anorchidism are extremely rare; more often such states are acquired. There will be no occasion to use these terms. In this paper I shall use the following classification:

Cryptorchidism: A. Mal descent or nondescent: abdominal, inguinal, superficial inguinal, pubic, high scrotal. B. Ectopy: perineal, penile, femoral.

In my interpretation of the literature, a testicle at the internal ring is considered abdominal, and one at the external ring or protruding from the external ring is considered inguinal. "Superficial inguinal" refers to the type of testis which is found at operation to have made its exit from the external ring and then passed superficial to the external oblique muscle of the abdomen for varying distances toward the anterior superior spine of the ilium, coming to lie between the superficial fatty

layer and the aponeurosis of the external oblique muscle. In the German literature this is known as the preinguinal location. I am aware that the superficial inguinal cryptorchidism may logically be, and sometimes is, classed as ectopy. "Pubic" refers to the testicle which has escaped from the external ring and has not passed low enough into the scrotum to escape pressure between an external force and the pubic bone. "High scrotal" is self explanatory. Since any tumor developing in a high scrotal testicle could hardly be distinguished from one arising in a normally descended testicle and since the effects of external violence would rarely compress such a testicle against the pubic bone, a high scrotal testicle will be considered as normal in this discussion. For practical purposes superficial inguinal cryptorchidism will be grouped together with inguinal cryptorchidism proper. No report was found in which a malignant growth in an inguinal testis was described as being superficial to the external oblique muscle of the abdomen. Undoubtedly such cases have occurred; it would seem that the surgeon could easily distinguish whether the external oblique muscle lay over or below the tumor, but so far as I know, this detail has not been published in the papers on malignant change in the inguinal testicle.

Bulkley was one of the writers who felt that the abdominal testis did not often undergo malignant change. He stated that malignant growth occurred in about 1 abdominal testis in 75. He calculated as follows: In the literature he found (as stated earlier) records of 182,729 male patients with 3 cases of malignant growth in the abdominal testicle, that is, about 1 to 60,000. Then he quoted the figures of Marshall (from Koenig) and those of Rennes (from Monod and Terillon). The former found 12 cryptorchids among 10,800 recruits and the latter 6 among 3,600; together, these results made a total of 18 to 14,400, or 1 to 800. The figure 60,000 divided by 800 gave a quotient of 75. However, there is no evidence that Marshall and Rennes were referring to abdominal retention; hence the two sets of figures do not admit of comparison.

I have obtained photostatic copies of several pages (82, 83, 207) of Marshall's book. He wrote:

. . . In some individuals both testicles are not in the scrotum. During the examination of 10,800 recruits, I found five in whom the right, and six in whom the left, testicle was not apparent. I have met with only one instance where both testicles had not descended.

This is not clearcut, but it is doubtful whether one is entitled to conclude that all these were cases of abdominal retention. Koenig quoted Marshall as follows:

Bei Erwachsenen fand Marshall unter 10800 Recruten Kryptorchismus 1 mal, Monorchismus 5 mal rechts und 6 mal links. (Among 10,800 adult recruits,

Marshall found cryptorchidism once, monorchidism five times on the right and six times on the left.)

Bulkley interpreted *Kryptorchismus* and *Monorchismus* as meaning abdominal retention and wrote:

. . . We must conclude, therefore, that the abdominally situated testicle is relatively immune to malignant changes.

This is an outstanding example of a widely quoted error arising from differing definitions.

Hospital Incidence Versus Private Practice Incidence.—In several instances, authors have drawn conclusions from but a part of their total experience. They have given figures for their hospital experience and neglected to give comparable figures for their private cases. Thus, several writers have seen more cases of testicular cancer in their private practice than in their hospital series. They have told how many patients were admitted to the hospital but not how many patients were observed in their private practice. Often the hospital is a specialized institution, yet the figures obtained there are offered with the implication that they represent a cross section of the entire population. A more representative figure would probably emerge from the private series. In any event, the entire experience of the writer should be offered rather than just a segment.

For example, almost every writer quotes Eccles, Kocher and Coley. Eccles saw 854 undescended testes with no malignant growths; in 1919 Coley reported 1,357 with no malignant growths; Kocher saw 1,000, in 1 of which there was malignant change. Together these men recorded 3,211 undescended testicles, in only 1 of which there was a malignant process. Of the 3,646 cases of undescended testes assembled by Hinman in 1936, these three reports contributed the great majority. Yet Coley elsewhere in his paper records 12 undescended testes in a total of 64 cases of sarcoma of the testis. Eccles mentions that in 1 of 40 cases of sarcoma the growth was in an abdominal testicle. It can readily be imagined that Kocher in his long career as a surgeon saw more than 1 case of malignant growth in an undescended testicle. It is misleading to accept one series and not the other. Probably these three much quoted but essentially misleading series should be discarded if one is to obtain an accurate idea of the facts.

Neglect to Indicate in Which Cases the Condition Was Bilateral.—Since failure of descent may affect either one or both testes and since malignant degeneration also may be unilateral or bilateral, more informative figures are gained by multiplying the number of patients by 2, for then the cases in which the condition was bilateral achieve their true significance.

STATISTICS

As a preliminary step in the study of the incidence of malignant growth in undescended testicles, it was necessary to learn how frequently nondescent or partial descent occurred. Several writers have referred to the figures obtained from examination of the Austrian army (1887) and of the American drafted army (1917 and 1918). Gilbert and Hamilton furnished some of the tables on which their figures were based. One of these is given in table 1 with the addition of the figures of Rennes. The resultant figure for incidence, 0.23 per cent, seems to be as accurate a figure as can be obtained. It is lower than the figure based on hospital admissions; this shows once again that the population of a general hospital is not typical of the entire population. It may be concluded that about 2 men in 1,000 have maldescent of the testicle and that 1 of about every 500 men is a cryptorchid.

TABLE 1.—*Incidence of Nondescent of Testicle in Army Recruits*

Author	Recruits Examined	Source	Recruits with Nondescent	
			Number	Per Cent
Marshall (1828).....	10,800	British and French armies.....	12	0.102
Rennes (1831).....	3,600	French army.....	6	0.16
Myrdacz (1887).....	6,962,543	Austrian army (1870-1892).....	14,057	0.2
Love and Davenport (1920).	2,754,164	American drafted army (1917-1918)	8,538	0.31
Southam and Cooper (1927)	10,000	Scottish recruits (1916-1917).....	52	0.5
Total.....	9,741,097	22,665	
Average.....				0.23

A figure which has shown but little variation through the years is the percentage of those with some degree of maldescent who have malignant growth in the testicle. This figure ranges from 7.5 to 15; in the series shown in table 2 it is 7.8. I have collected 1,422 cases of testicular malignant growth from the literature; 165 (11.6 per cent) of the patients were cryptorchids. Gilbert and Hamilton amassed over 7,000 cases of tumor, and 840 (over 11 per cent) of the patients were cryptorchids. The difference between 0.23 ± 0.0015 per cent (table 1) and 11.0 ± 0.3 per cent is so significant that it may be concluded without fear of controversion that the malignant process is more likely to affect the maldescended organ.

To approach this from another aspect, I collected from the literature reports on 1,413 patients with undescended testicles (table 3); in 22 of these maldescent was associated with malignant change in the testicle. In some reports it is not clear how many testicles were involved; in some cases the condition was undoubtedly bilateral. The incidence of malignant change was found to be 1.5 ± 0.3 per cent—much higher than is gen-

erally concluded from collected series. This is because the large and misleading series of Eccles, Coley and Kocher have been excluded. Of the 500,000 patients in table 2, malignant degeneration of the scrotal testicle occurred in 362, an incidence of 0.07 ± 0.003 per cent. The difference between 1.5 ± 0.3 and 0.07 ± 0.003 is 1.43 ± 0.32 per cent. This difference, which is more than four times its standard error, confirms the conclusion that the undescended testicle is more liable to be affected by malignant change.¹ I hasten to add that this does not prove that the malposition caused the malignant change. It merely indicates that the difference is greater than one would expect from chance and that thus there is some causal agent operating. It is likely that

TABLE 2.—Incidence of Malignant Testicular Tumor

Author and Date	Admissions of Male Patients	Malignant Testicular Tumors			
		Total Number	Scrotal	Abdominal	Inguinal
Eccles (1903).....	84,000	40	39	1	0
Howard (1907).....	110,000	65*	56	0	8
Coley (1908).....	59,000	34	31	3	0
Bulkley (1913).....	13,000	13	11	2	0
Southam and Linell (1923).....	57,000	38	34	3	1
MacKenzie and Ratner (1934).....	65,000	26	23	1	2
Hinman and Benteen (1936).....	39,000	40	37	3	0
Christofferson and Owen (1940).....	28,000†	119	114	0	5
Campbell (1942).....	50,000†	19	17	1	1
	505,000	394	362	14	17
Percentage of 500,000.....		.078	.072		
Percentage of 394.....			91.8	3.5	4.3
Percentage of 31.....				45	55

* In 1 of the patients the "retained" testis was "just below the external ring."

† This figure represents an estimation of the number of patients admitted.

the same factor which caused the failure of descent also causes the malignant degeneration. More and more cases are being recorded of malignant change occurring in testes which have been placed in the scrotum. Eventually, statistical analysis of these cases may throw some light on the malignant process in general. From among the 500,000 male patients admitted to the hospitals there were 14 with malignant growth in the abdominal testicle and 17 with malignant growth in the inguinal testicle. In an exhaustive survey, Gilbert and Hamilton found records of 345 cases of malignant growth in the abdominal testicle and 490 cases of malignant growth in the inguinal testicle. The percentages are almost identical, 45 and 55 in my series, and 41.3 and 58.7 in theirs.

1. It should be stated that if the incidence is computed on the basis of number of testicles, a figure of even greater statistical significance is obtained. Not more than 20 per cent of the patients with undescended testicles had bilateral non-descent, while almost all of the 500,000 patients had bilateral descent.

The incidence shown in table 3 is much larger than that generally reported from collected series. I believe that this is because the often quoted series of Eccles, Coley and Kocher are essentially misleading; they have therefore been excluded. Approximately the same incidence (1 to 50) is obtained from calculations with the figures in table 6 and confirms the major conclusion arrived at by another approach from the data in table 2, that is, that the undescended testicle is much more liable to malignant change than the normally placed organ. Thus by three different approaches the same conclusion is obtained. The confusion of former years disappears.

TABLE 3.—Incidence of Malignant Growth in Nondescended Testicle

Author	Patients with Undescended Testicles	Patients with Malignant Growth in Undescended Testicles
MacKenzie and Ratner.....	105*	3
Hinman and Benteen.....	155	3
Southam and Linnell.....	413	4
Hoffstatter.....	181	4
Keyes (in discussion on Cunningham).....	40	0
Thiessen and Walters.....	96	0
Counseller.....	112	0
Owen.....	20	5
Campbell.....	158	2
Brenner.....	75	0
Goritz.....	57	1
	1,413	22
Ratio.....		1:64
Percentage.....		1.5

* This figure is taken from the paper covering a ten year period. The 3 patients with malignant growth in the undescended testicles were encountered in the succeeding three years and hence the actual period covered is thirteen years. Thus the figure of 105 (about 10 per year) should be expanded to about 135. This would make no great difference in the incidence, however, and would not alter the conclusions reached.

Table 4 comprises all the reports I could find (except one or two papers in which the protocols were too meager) which offered figures to show the relative incidence of abdominal and inguinal maldescent. Abdominal maldescent accounts for 14.3 per cent of all the cases. The difference between 41.3 ± 1.7 per cent (from Gilbert and Hamilton's series of cases of malignant growth in the undescended testicle) and 14.3 ± 0.7 per cent is 27 ± 1.8 per cent, a figure which is fifteen times its standard error and therefore of enormous statistical significance. Gilbert and Hamilton stress the point, and I am inclined to agree, that most authors consider as abdominal a certain number of testicles which migrate back and forth between the abdomen and the inguinal canal and which are therefore properly to be considered inguinal. If Gilbert

and Hamilton's percentage of 10.8 is more nearly correct, then the susceptibility of the abdominal testicle to malignant change is even more marked than I have indicated.

There are those who may believe that a collective review does not give the actual comparative incidence of malignant change in the inguinal

TABLE 4.—*Relative Incidence of Abdominal and Inguinal Nondescend of Testicle*

Author and Date	Undescended Testicles				Abdominal
	Total Number	Inguinal	Superficial Inguinal	Pubic	
Bryant (1867).....	7	4	3
Eccles (1903).....	727	334	..	254	139
Odiorne and Simmons (1904).....	87	51	1	18	17
Burdick and Coley (1926).....	197	83	73	24	17
Brunzema (1929).....	132	122	7	..	3
Frühman and Sternberg (1930).....	192	87	77	..	28
Heinecke (1932).....	30	21	9	..	0
Counseller (1933).....	102	71	31
Thiessen and Walters (1935).....	96	43	..	35	18
Bjerre (1935).....	350	340	10
Wangensteen (1935).....	23	20	3
Campbell (1942).....	176	85	46	12	33
Total.....	2,119	1,261	213	343	302
Percentage.....		59.3	10.0	16.4	14.3

TABLE 5.—*Proportion of Cases of Malignant Growth in Abdominal and in Inguinal Testicles in the Same Hospital*

Author	Cases of Testicular Malignant Growth	Cases of Malignant Growth in		
		Undescended Testicle	Abdominal Testicle	Inguinal Testicle
Authors in table 2.....	394	31	14	17
Odiorne and Simmons (1904).....	55	7	3	4
Cunningham (1921).....	67	0	0	0
Southam and Linell (outside cases) (1923)....	7	3	2	1
Lower (Higgins) (1928).....	23	1	0	1
Rea (1931).....	76	11	6	5
Taylor (1938).....	50	15	8	7
Total.....	672	68	33	35
Percentage.....		10.1	48.5	51.5

and in the abdominal testicle. Accordingly, I have gathered together from the literature papers which present the number of malignant growths in the inguinal and in the abdominal testicle from the same hospital. In this series of 672 malignant testicular tumors there were 68 in undescended testicles (10.1 per cent); of these 33 were abdominal and 35 inguinal, that is, 48.5 to 51.5 per cent. Again the proportion is the same. The difference between 48.5 ± 6.0 per cent and $14.3 \pm$

0.7 per cent is 34.2 ± 6.1 per cent, a figure which is more than five times its standard error and therefore statistically very significant.

It will be of interest to carry out the same calculations that Bulkley attempted. Of the 500,000 male patients admitted, 14 had malignant growth in the abdominal testicle, that is, 1 in about 36,000. Five of the nine papers gave the incidence of undescended testis as 930 in about 240,000 patients admitted, or 1 to 256. One may estimate that the percentage of abdominal testicles was 14.3 (table 3). This would make 133 abdominal retentions in 240,000 male patients admitted, or about 1 in 1,800. By dividing 36,000 by 1,800 one gets a quotient of 20, indicating that 1 abdominal testicle out of 20 undergoes malignant change.

Making the same calculations regarding the inguinal testicle, one finds that 1 male patient in 30,000 has malignant growth of the inguinal testicle; and that 1 male patient in 365 has inguinal testicle. By dividing

TABLE 6.—*Incidence of Nondescent of Testis in Hospital Admissions*

Author	Location	Admissions of Male Patients	Admissions for Undescended Testis
MacKenzie and Ratner.....	Montreal	50,000	105
Hinman and Benteen.....	San Francisco	39,359	155
Owen and Christoffersen.....	Illinois	28,000	15
Southam and Linell.....	Manchester	57,000	413
Young.....	Baltimore	12,500	60
Campbell.....	Boston	50,000	182
Total.....		236,859	930
Ratio.....			1:256

30,000 by 365 one gets a quotient of 82, indicating that 1 inguinal testicle of about 80 undergoes malignant change. The difference is between about 1 per cent and about 5 per cent. Taken together, there are 2 malignant growths to about 100 undescended testicles, a ratio which is of the same order of magnitude as the (1:64) shown in table 3.

COMMENT

While most writers have recognized that the undescended testicle is more prone to undergo malignant change, they disagree widely as to whether the inguinal or the abdominal testicle is the more liable to undergo such a change. The majority have inclined to the belief that the abdominal testicle is less liable to be affected by the malignant tendency, and this is reflected in the practice of putting the inguinal testicle back into the abdomen if it cannot be brought down into the scrotum. It has been thought that the inguinal testicle was more exposed to trauma.

A study of the tables and their accompanying notes will indicate that the incidence of nondescent in the general adult male population is

0.23 \pm 0.0015 per cent and that the incidence of nondescent in cases of malignant growth in the testis is 11.0 \pm 0.3 per cent. The difference is 10.77 \pm 0.33 per cent, a figure which is thirty-two times its standard error. Of over 2,000 undescended testicles, the abdominal constitute 14.3 \pm 0.7 per cent of the total, and of 840 undescended testicles involved in malignant growth the abdominal constitute 41.3 \pm 1.7 per cent. The difference is 27 \pm 1.8 per cent, a figure which is fifteen times its standard error. Hence one may say that data now available are sufficient to enable one to conclude unequivocally that the undescended testicle is more liable than the scrotal to malignant change and that the abdominal testicle is more liable to malignant change than the inguinal.

On the basis of accumulated statistical data, it is suggested that the practice of placing the inguinal testicle within the abdomen should be abandoned altogether. The abdominal testicle should always be explored and brought to the scrotum if possible, or at least into the inguinal canal. If neither of these improvements can be accomplished, the testicle should be excised. Malignant change in the abdominal testicle proceeds to the inoperable stage before the patient is aware of any enlargement.

Some may argue that it is not wise to operate on 20 abdominal testicles to prevent cancer in 1. Were it not that there are associated conditions which often indicate operation, I should be inclined to agree. However, hernia is frequently associated,² and during the operation for this, the testis should be brought into a region where it is palpable or excised. There are often psychologic reasons also why it is best to try to place the testis in the scrotum.

To carry this program into effect in a case of bilateral abdominal testicle is admittedly most difficult. There is convincing evidence that the man with bilateral maldescent is in much greater danger from cancer than the man with but one nondescended testicle. All are agreed that nondescent and cancer are more common in the right testicle. While there are no figures to support the hypothesis, it seems likely that of two abdominal testicles the left would ordinarily be nearer the internal ring and therefore more capable of being brought into the canal. If the other testicle cannot be brought into the canal, it should be excised. Of course, no surgeon would recommend bilateral excision to prevent cancer, but it seems that the testes should (and in most instances can) be brought at least into the inguinal canals. Thereafter, the patient with undescended testicle, whether the subject of orchiopexy or not, should be observed by his physician at frequent intervals. There is no evidence, as yet, that

2. Of the 34 abdominal testicles observed at the Peter Bent Brigham Hospital, 14 were associated with hernia on the same side and 3 with hernia of the opposite side, the opposite testicle being normally descended.

orchiopexy prevents cancer; further data must accrue. The proved overwhelming susceptibility of the undescended testicle to malignant change should make such a testicle the object of unrelenting suspicion.

SUMMARY

Six reasons why confusion has existed in the literature on undescended testicle are: (1) lack of knowledge of the statistical method on the part of physicians; (2) the serious misquotation of one author by another; (3) failure to use a uniform nomenclature; (4) the tendency to depend on isolated or selected series; (5) the continuing influence of papers written in an earlier period, when the abdomen was infre-

TABLE 7.—*Undescended Testicles at the Peter Bent Brigham Hospital from 1913 to 1939 in About 50,000 Male Patients*

Type of Undescended Testis	Testicles Showing No Malignant Change			Testicles Showing Malignant Growth			Total
	Right	Left	Total	Right	Left	Total	
Abdominal.....	17	16	33	1	..	1	34
Inguinal.....	43	42	85	..	1	1	86
Superficial inguinal.....	26	20	46	46
Pubic.....	7	5	12	12
High scrotal.....	2	1	3	3
Perineal.....	0	1	1	1
Total.....	95	85	180	1	1	2	182*

* This represents 183 patients; 24 had bilateral nondescent of testicle. Of the 2 patients with malignant growth in the undescended testicles, 1 had bilateral inguinal nondescent of testicle.

quently explored; (6) the neglect to indicate in which cases the condition was bilateral because patients rather than testes are enumerated.

The earlier literature has been investigated and the original contributions have been consulted in each case. Many of the earlier ideas about malignant change in the undescended testicle resulted from the failure of authors to consult original sources.

From the literature since 1900 there have been collected: (1) a group of about 500,000 cases in which male patients were admitted to hospitals; (2) a series of 1,413 cases of undescended testicle in which the incidence of malignant change is known; (3) a series of 2,119 cases of undescended testicle in which the relative incidence of abdominal and inguinal nondescent is known; (4) a series of 672 cases of malignant growth in the testis in which the relative frequency of abdominal and inguinal nondescent is known.

Table 7 lists all cases of nondescent at the Peter Bent Brigham Hospital for a period of twenty-seven years.

CONCLUSIONS

From the data presented the following conclusions may be drawn :

The incidence of malignant change in the testicle is statistically higher in undescended testicles than in normally descended testicles.

Inguinal nondescent is more frequent than abdominal nondescent. In series including children, the incidence of abdominal nondescent constitute about 10 per cent of the total incidence of nondescent; in series with few or no children, the incidence of abdominal nondescent constitutes about 20 per cent.

The incidence of malignant growth in the testicle is statistically higher in cases of abdominal nondescent than in cases of inguinal nondescent. One in about 20 abdominal testicles shows malignant change. One in about 80 inguinal testicles shows malignant change.

Combined hospital figures reveal about equal numbers of abdominal and inguinal malignant growths. This is because the proportion of inguinal to abdominal testicles is about 4 to 1 and the proportion of cancerous inguinal to cancerous abdominal testicles is about 1 to 4.

Dr. F. A. Simeone, Urologic Fellow the Peter Bent Brigham Hospital, suggested the necessity of a statistical study of the literature.

Dr. J. B. Hamilton of the Yale University School of Medicine furnished the tables and the bibliographic lists used in preparing the paper written by him and Dr. J. B. Gilbert.

730 Monaco Boulevard.

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TREATMENT OF URETERAL SPASM

OBSERVATIONS WITH SPECIAL REFERENCE TO THE USE OF
EXTRACT OF MAMMALIAN SKELETAL MUSCLE

PAUL LIONEL GETZOFF, M.D.

GILBERT CHARLES TOMSKEY, M.D.

AND

HILAIRE DUBERTRANDE OGDEN JR., M.D.

NEW ORLEANS

The necessity for preserving the normal peristaltic activity of the ureter and thereby maintaining an undisputed right of way for the passage of the urine from the kidneys to the bladder has been accepted as an incontrovertible fact.

In his splendid publications on the physiology of the ureter, Trottn¹ has pointed out that this structure can be conveniently separated into three divisions—upper, middle and lower thirds. This division is based on the results of his physiologic and pharmacologic studies. Progressive peristalsis may commence in any of these divisions; eventually, the peristaltic activity will spread throughout the remainder of the ureter. If the ureter is unable to convey its contents to the bladder and this adynamic status prevails relatively long, then renal damage is an inevitable consequence. Such incidental accessory factors as gravity, descent of the diaphragm and transmitted renal filtration pressure are capable of aiding in the passage of urine through the ureter only in the presence of normal peristaltic activity in that organ. It is evident that normal ureteral peristalsis is as indispensable to the preservation of function of the renal parenchyma and calyceal system as the maintenance of the ureteral path free of mechanical obstruction.

INSULIN-FREE PANCREATIC EXTRACT

In 1926, Frey and Kraut² published a report of the isolation of a substance from urine which produced vasodilatation. It was suggested

From the departments of urology of the Louisiana State University School of Medicine and the Charity Hospital.

1. Trottn¹, H. R.: Graphic Registration of the Function of the Human Ureter with the Hydrophoragraph, *J. Urol.* **28**:1-33, 1932.

2. Frey, E. K., and Kraut, H.: Action on Heart of New Circulatory Hormone Found in Urine, *Arch. f. exper. Path. u. Pharmacol.* **133**:1-56, 1928.

that this substance was secreted by and conserved in the pancreas, excreted in an inactive state into the circulation and finally excreted in an activated state by the kidneys. The depressor effect of this substance was attributed by Wolffe³ to its property of neutralizing the pressor effect of epinephrine by moderating the sensitivity of the sympathetic nervous system. This was based on the premise that angiospasm was the effect of an imbalance of the sympathetic and parasympathetic nervous systems with ultimate predominance of the former.

Ten years later, Joseph Lazarus⁴ reported the successful use of an insulin-free extract of pancreatic tissue in the treatment of occlusion of the ureter due to calculi and spastic conditions. The hypothesis on which this clinical experiment was founded was that excessive stimulation of the extrinsic and the intrinsic sympathetic nerve fibers occurred in the ureteral segment in which a calculus was lodged. Spasticity of the ureteral musculature in the contiguous wall followed this chain of events. Reviewing the satisfactory clinical results obtained by Wolffe, Findley and Dessen, who treated angina pectoris and spastic colitis with this depressor pancreatic extract, Lazarus was impressed with the possibilities of applying the same substance to sympathetic hyperactivity in the ureter in the presence of foreign bodies and various inflammatory changes. His results were encouraging, and in 1940 he reported uniformly good effects from the use of pancreatic tissue extract in more than 100 cases of ureteral occlusion due to calculi, spasm and stricture.

Carroll and Zingale⁵ also published an account of their results in the treatment of renal colic with insulin-free extract of pancreatic tissue. They attributed the pain in renal colic (not always due to distention of the proximal ureteral segment) to ischemia of the nerve endings present at the site of ureteral muscle spasm. They contended that pancreatic extract relieves this ischemic state by producing relaxation of the affected portion of the ureter, thus permitting the affected part to return to its normal physiologic status.

3. Wolffe, J. B.; Findlay, D., and Dessen, E.: Treatment of Angina Pectoris with Tissue Vasodilator Extract: Preliminary Report, *Ann. Int. Med.* **5**:625-642, 1931.

4. Lazarus, J. A.: Use of Insulin-Free Pancreatic Tissue Extract as Aid in Cystoscopic Treatment of Impacted Ureteral Calculi and Spastic Occlusions of Ureter: Preliminary Report, *Urol. & Cutan. Rev.* **40**:847-850, 1936; Further Observations on the Use of Insulin-Free Pancreatic Tissue Extract as Aid in Cystoscopic Treatment of Impacted Ureteral Calculi and Spastic Occlusions of Ureter, *J. Urol.* **43**:102-107, 1940.

5. Carroll, G., and Zingale, F. G.: A Clinical and Experimental Study of the Effect of Pancreatic Tissue Extract on the Ureters, *South. M. J.* **31**:233-236, 1938.

EXTRACT OF MAMMALIAN SKELETAL MUSCLE

In 1930, Ludwig Haberlandt,⁶ while engaged in working out a research problem on frogs, noted the efficiency of Ringer's solution in eliciting an accelerated ventricular rate in the isolated ventricle in which the resected sinus had been left to beat. He demonstrated the presence of an active substance which he termed "cardiac hormone." This substance was proved to have the property of making a frog's heart beat again after it had remained in a dormant condition for two or three days. Numerous clinical applications of this substance were then attempted. Julius Bauer of Vienna reported some favorable results in treating angiospastic conditions with the so-called heart hormone. Clinicians throughout Europe became interested in the implications of Haberlandt's work. Gley and Kisthinios,⁷ M. Schwartzman,⁸ Fahrenkamp,⁹ Korach,¹⁰ Y. S. Shwartzman,¹¹ Nielsen,¹² Giroux,¹³ Dimitracoff¹⁴ and numerous others began to use various tissue extracts in the treatment of cardiovascular diseases, particularly hypertension, angina pectoris, endarteritis and angiospastic states.

According to the same reasoning by which Lazarus applied insulin-free pancreatic extract in the treatment of ureteral obstruction and spasm, it was felt worthy of the effort to study an extract of mammalian skeletal musculature in order to learn whether this extract possessed further pharmacologic properties analogous to the pancreatic extract, especially as related to the treatment of obstructive anomalies of the ureter.

Description.—In this study, we employed an extract of mammalian skeletal muscle which consists mainly of nucleosides derived from nucleic

6. Haberlandt, L.: Cardiac Hormone, *Wien. med. Wchnschr.* **81**:527 and 566, 1931; Cardiac Hormone, *Endokrinologie* **6**:335-345, 1930.

7. Gley, P., and Kisthinios, N.: Existence of Blood Pressure Reducing Pancreatic Hormone, *Wien. klin. Wchnschr.* **43**:1530-1536, 1930.

8. Schwartzman, M. S.: Muscle Extract Treatment of Grave Vascular Diseases, *Brit. M. J.* **1**:492-493, 1931.

9. Fahrenkamp, K.: Cardiokinetic Muscle Extract in Treatment of Angina Pectoris, *Aerzt. Rundschau* **41**:7-9, 1931.

10. Korach, E.: Causal Therapy with Myoston (Cardiokinetic Muscle Extract) in Angina Pectoris and in Essential Hypertension, *München. med. Wchnschr.* **78**:473-474, 1931.

11. Shwartzman, Y. S.: Action of Cardiokinetic Extract from Skeletal Muscles on the Cardiovascular System, *Wien. klin. Wchnschr.* **44**:768-779, 1931.

12. Nielsen, O. J.: Therapeutic Application of Lacarnol (Cardiokinetic Muscle Extract), *Ugesk. f. læger* **93**:240-243, 1931.

13. Giroux, R., and Kisthinios, N.: Insulin-Free Pancreatic Extract in Raynaud's Disease, *Bull. méd., Paris* **45**:140, 1931.

14. Dimitracoff, C.: Insulin-Free Extract of Pancreas in Obliterating Arteritis, *Crón. méd. mex.* **29**:559-566, 1930.

acid. This solution is biologically standardized so that its content has a uniform amount of active nucleosides. It does not contain any choline, histamine, epinephrine or related substances; it is free of pharmacologically significant amounts of potassium or calcium ions. This extract has been found effective in the treatment of angina pectoris and various other angiospastic conditions. Experimental evidence indicates that tissue extracts derived from mammalian skeletal muscles dilate the coronary vessels of mammalian hearts, thereby increasing the rate of flow through them. Ludwig¹⁵ has reported a slight acceleration of the pulse with no change in the electrocardiogram when this muscle extract is given intravenously to healthy persons. Buchholz¹⁶ reported that even large doses had practically no effect on normal hearts; he noted slight redness of the face and subjective sensation of warmth. In collaboration with Cziike, Buchholz observed the action on the respiratory apparatus and reported that inspiration and expiration became easier and that the residual air was diminished. We have not been able to find any reports of undesirable toxic reactions or cumulative effects following the use of this extract.

Dosage.—The selected extract was given hypodermically and intramuscularly in doses of 1.0 and 2 cc. In several cases the drug was given in repeated doses (i. e., every four hours for four doses). The preparation for oral administration was not used in this experiment.

Clinical Applications.—In the period from January 1941 to May 1941, during which this study was conducted, 17,000 patients were admitted to the Charity Hospital. Of this number there were admitted to the urologic service 315 white males, 80 white females, 390 Negro males and 94 Negro females. No notable differences were observed in the response of white and Negro or male and female patients.

The muscle extract was administered for the relief of pain to patients with a wide variety of urologic complaints. These included: acute pyelonephritis (9 cases); chronic pyelonephritis (32 cases); ureteral colic due to calculi (27 cases); ureteral colic with which no calculus could be demonstrated by roentgen examination (5 cases), and post-cystoscopic reactions (3 cases). Slight or no relief was noted from the treatment of acute pyelonephritis (3 cases), chronic pyelonephritis (6 cases), ureteral colic due to calculi (8 cases), ureteral colic with which the presence of calculi could not be demonstrated by roentgen examination (3 cases) and ureteral spasm (5 cases).

15. Ludwig, W.: Clinical Investigation of the Effects of Cardiac Skeletal Muscle Extract on Diseases of the Circulatory System, *Klin. Wchnschr.* **80**:1531, 1931.

16. Buchholz, B.: On the Clinical Experience with the Cardiac Hormone, *Lacarnol, Deutsche med. Wchnschr.* **57**:188-190, 1931.

Therefore, in a total of 91 cases of diverse urologic conditions, the muscle extract was administered for the alleviation of pain. In 66 cases (72.5 per cent) appreciable to complete relief was obtained, and in 25 cases (27.5 per cent) there was failure to obtain any desirable degree of relief.

No sedation was employed until it was obvious that the muscle extract was of no value in the case.

The average time for the relief of pain was six and one-half minutes. In this connection, we have noted that no desirable effects from the muscle extract can be anticipated if relief is not obtained within ten minutes.

Several interesting points were brought out in connection with this series. One patient who had attacks of angina pectoris associated with acute exacerbations of chronic pyelonephritis obtained relief for both

TABLE 1.—*Results of the Administration of Extract of Mammalian Skeletal Muscle for the Relief of Pain*

Conditions Treated for the Relief of Pain	Appreciable to Complete Relief (Cases)	Slight to No Relief (Cases)	Total Cases
Acute pyelonephritis	6	3	9
Chronic pyelonephritis	26	6	32
Ureteral colic due to calculi (presence of calculi proved by roentgen examination).....	19	8	27
Ureteral colic (presence of calculi not proved by roentgen examination)	2	3	5
Ureteral spasm	10	5	15
Postcystoscopic reaction	3	0	3
Total.....	66	25	91

conditions every time that she received an injection of the skeletal muscle extract. Another patient who suffered severe attacks of renal colic and persistent epigastric pain (peptic ulcer demonstrated in gastro-intestinal series) was completely relieved of discomfort after injections on four separate occasions.

Two errors in diagnosis also are included in this series. One patient who had suffered from pain believed due to a possible chronic pyelonephritis failed to obtain any relief following two injections of the extract. Further study revealed that the pain was due to an ovarian cyst; when this was excised, the pain disappeared. Another patient who gave a history suggestive of renal colic failed to obtain any relief from injections of the extract. She later proved to have colitis. Two patients with renal colic (proved by roentgen examination to be due to calculi) passed calculi within thirty minutes after the injection of the muscle extract.

Eighty-two cystoscopic examinations were performed; after this procedure, 1 to 2 cc. of muscle extract was routinely given hypodermically.

The following conditions were included in this series: acute pyelonephritis (3 cases), chronic pyelonephritis (28 cases), hydronephrosis (3 cases), infected hydronephrosis and pyonephrosis (4 cases), nephrop-tosis (2 cases), perinephric abscess (2 cases), ureteral colic due to calculi (19 cases), ureteral colic in which no calculi were demonstrated by roentgen examination (3 cases), abnormal insertion of the ureter (4 cases), ureteral spasm (9 cases), ureteral kink with hydronephrosis (1 case), ureteral stricture (13 cases), carcinoma of bladder (2 cases),

TABLE 2.—*Reaction and Nonreaction After Cystoscopic Examination with Routine Administration of Muscle Extract After This Procedure in Eighty-Two Cases*

Condition	Cystoscopic Examinations After Which There Was		Total Examina- tions
	No Post- cystoscopic Reaction	Post- cystoscopic Reaction	
Acute pyelonephritis	3	0	3
Chronic pyelonephritis	28	0	28
Hydronephrosis	3	0	3
Infected hydronephrosis and pyonephrosis.....	4	0	4
Nephrop-tosis	2	0	2
Perinephric abscess	2	0	2
Ureteral colic due to calculi (presence of calculi proved by roentgen examination).....	17	2	19
Ureteral colic (presence of calculi not proved by roent- gen examination)	2	1	3
Abnormal insertion of ureter.....	3	1	4
Ureteral spasm	8	1	9
Ureteral kink with hydronephrosis.....	1	0	1
Ureteral stricture	12	1	13
Carcinoma of the bladder.....	2	0	2
Carcinoma of the cervix vesicae with extension into the bladder	5	1	6
Chronic cystitis	14	1	15
Hodgkin's disease	1	0	1
Tuberculous nephritis	2	0	2
Hypernephroma	1	0	1
Total.....	110	8	118

carcinoma of the cervix vesicae with extension into the bladder (6 cases), chronic cystitis (15 cases), Hodgkin's disease (1 case), tuberculous nephritis (2 cases) and hypernephroma (1 case).

Postcystoscopic reactions occurred in 1 case of each of the following urologic conditions: ureteral colic in which no calculus was demonstrated by roentgen examination, abnormal insertion of the ureter, ureteral spasm, ureteral stricture, carcinoma of the cervix vesicae with extension into the bladder, and chronic cystitis. Postcystoscopic reactions also occurred in 2 cases of ureteral colic due to calculi.

Therefore, in a series of 82 cases in which cystoscopic examinations were made and in which muscle extract was administered routinely after the procedure was completed, there were 8 (9.8 per cent) instances

of postcystoscopic reactions and 74 (90.2 per cent) cases in which no postcystoscopic reactions occurred.

In this series, there were 6 cases in which one or both ureters could not be catheterized because of marked spasm. From 1 to 2 cc. of the muscle extract was then given to the patients intramuscularly; after this injection (average time six and one-half minutes) it was possible to introduce catheters up the ureters with relative ease. In 1 patient in this series who had had several pelvic lavages at intervals of six weeks marked cystoscopic reactions always developed. Before the last three cystoscopic treatments, she received 1 cc. of muscle extract hypodermically and she suffered no postcystoscopic reactions.

Controls.—Mammalian skeletal muscle extract in 1 cc. doses was injected hypodermically into 20 patients with electrocardiographic evidence of myocardial disease for the purpose of studying the effect on blood pressure. The findings may be summarized as follows:

1. No appreciable lowering of blood pressure occurred in patients with normal blood pressure.

2. Notable drop in blood pressure occurred only in cases of hypertension; the systolic pressure underwent a greater decrease than the diastolic pressure. This drop in blood pressure was governed by two factors:

- (a) The younger patient sustained a greater drop in blood pressure for a longer period than the older patient with the same basal blood pressure.

- (b) The greater the degree of hypertension, all other factors being equal (e. g., age, cardiac status), the greater the drop in blood pressure after the administration of the drug.

3. The lowered blood pressure that occurred after the injection of muscle extract persisted from forty minutes to sixteen hours.

4. In no case was the induced lowering of blood pressure followed by any subjective complaints (e. g., vertigo, headache), loss of consciousness or cardiac decompensation.

We believe that the explanation for the blood pressure findings just summarized rests on the premise that the mammalian muscle extract used in this study tends to bring about a relaxation of the smooth musculature in the entire body. This hypothesis enables us to explain why the degree of lowering of the blood pressure and sustenance of the reduced level is greater in younger patients, in whom sclerotic changes in the vascular walls tend to be less pronounced, than in the older patients.

It should be noted that reduction of the blood pressure with extract of mammalian muscle has not been a universally consistent finding. An editorial in *Lancet* commented on the use of tissue extracts as follows: "As regards hypertension, opinions are diverse. Some record definite

lowering of pressure with considerable clinical improvement; others using the same preparations have seen little or no effect."

Finally, skeletal muscle extract (1 cc. hypodermically) was given to children, patients with cardiac decompensation, patients with demonstrable hepatic and renal disease and patients subject to attacks of bronchial asthma (not during attacks). In no instance were we able to demonstrate any undesirable side reactions, either immediate or delayed.

SUMMARY

Some of the experimental and clinical observations with insulin-free pancreatic extract and extract of mammalian muscle are reviewed.

An extract of skeletal mammalian muscle was used for the purpose of relieving pain, preventing and treating postcystoscopic reactions in cases of diverse urologic conditions and relieving various obstructive anomalies of the urinary tract with encouraging results.

No undesirable clinical effects or side reactions were encountered with this mode of treatment.

The extract of mammalian skeletal muscle used in this study was supplied by the Winthrop Chemical Co., Inc.

RECONSTRUCTION OF THE STOMACH OUTLET IN GASTRIC RESECTION

A SIMPLE SUTURE FOR USE WITH THE BILLROTH 2 ORALIS TOTALIS TYPE OF OPERATION

HANS MAY, M.D.

PHILADELPHIA

The most popular procedure for anastomosing the stomach with the jejunum in the Billroth 2 type of gastric resection is the end to side anastomosis (terminolateral gastrojejunostomy), i. e., the Billroth 2 oralis totalis type. The operation has one disadvantage; the wide stomach outlet, consisting of the entire transverse section of the stomach, permits rapid emptying of the stomach and consequently considerable shortening of the second or gastric phase of digestion. Several methods have been suggested for narrowing the width of the anastomosis. Usually, the proximal half of the divided stomach is closed while the distal part is left open to be anastomosed with the jejunum (Billroth 2 oralis inferior), or the distal part is closed and the proximal half anastomosed (Billroth 2 oralis superior). This method leaves one weak point, and that is the meeting of the closed part and the anastomosis—the three corner point. Billroth aptly called this point *Jammerecke* (Wailing Wall). Lahey¹ protects this point by suturing the jejunal loop on the closed part of the stomach outlet. To eliminate this weak point, to simplify the procedure of narrowing the gastric transverse section and particularly to reconstruct the shape of the stomach to the most natural possible anatomic conditions, I recommend a simple procedure. No originality is claimed. Haberer² used a similar method in his modification of the Billroth 1 type of resection. With his device it is possible to narrow the transverse section of the stomach so far that it can be anastomosed end to end with the duodenum. I performed his operation twice and found it satisfactory. It was not difficult to transfer Haberer's modification to the Billroth 2 type of resection. However, I simplified the technic and thus changed it in some respects.

The operation is performed as follows: The stomach and the duodenum are exposed in the usual way. The vessels of the part to

From the Lankešau Hospital, service of Dr. George P. Müller.

1. Lahey, F. H., and Marshall, S. F.: *Technique of Subtotal Gastrectomy for Ulcer*, Surg., Gynec. & Obst. **69**:498, 1939.

2. Haberer, H.: *Gegenwärtiger Stand der operativen Behandlung des Magen- und Zwölffingerdarmgeschwürs*, Deutsche Ztschr. f. Chir. **200**:212, 1927.

be resected are ligated and separated. The stomach is separated between two soft clamps. Then follow the separation of the duodenum and the closure of the stump. The jejunum is brought in contact with the stomach in a retrocolic or an antecolic position, its afferent loop toward the lesser, its efferent loop toward the greater, curvature. Now the anastomosis between the transverse section of the stomach and the jejunum is made. In order to narrow the stomach outlet evenly throughout, a suture is recommended which will include more tissue on the gastric side than on the jejunal side, i. e., one that will produce a pleating in of the terminal stomach wall. The posterior stomach wall is shortened by a pleating-in serosa suture and the anterior wall by a pleating-in mucosa suture.

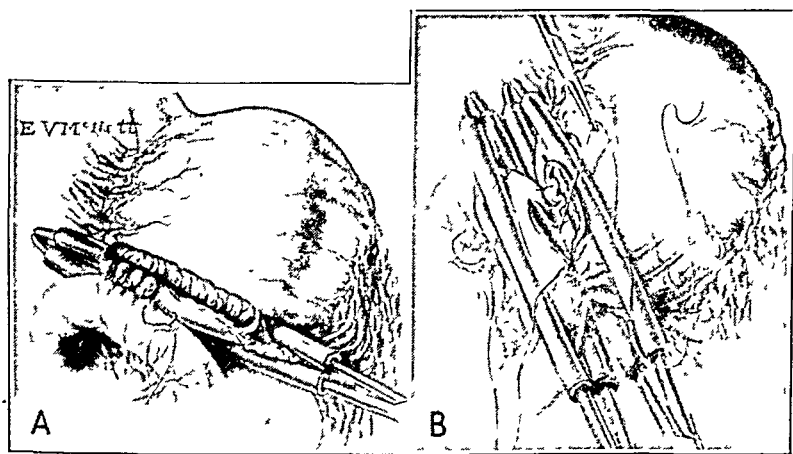


Fig. 1.—*A*, transverse section of the stomach to be anastomosed with the jejunum after the Billroth 2 oralis totalis type of gastric resection. The posterior serosa-muscularis suture is interrupted and led horizontally through the stomach wall and vertically through the jejunum, thus pleating in the posterior gastric wall. After two such sutures have been done, the stomach clamp is opened temporarily. *B*, the mucosa muscularis-serosa suture is continuous. To take the knot of this suture away from the corners of the anastomosis, i. e., to take away the weak points from the curvatures, the suture starts from the middle of the posterior wall. It closes first one half of the anastomosis, then the second half. Both sutures meet in the middle of the anterior wall. When either suture reaches the anterior wall, it becomes a pleating-in suture. In this drawing the half of the anastomosis toward the greater curvature is being closed. The "loop on the mucosa" type of suture is used. To shorten the gastric wall the loop on the gastric side is made wider than the loop on the jejunal side. Furthermore, the jejunal loops are placed close to each other. The pleating effect, if necessary, may be increased by leading the jejunal loop not horizontally but vertically through the jejunum.

The serosa suture between the posterior gastric wall and the jejunum commences at the lesser curvature and is interrupted. In order to include more tissue on the gastric side than on the jejunal side the

direction of the stitch is horizontal on the gastric and vertical on the jejunal side. The suture is led first through the serosa-muscle layer of the gastric wall parallel to the stomach outlet, i. e., horizontally, with a broad "bite" of tissue. It is then led through the jejunal serosa-muscularis right above the insertion of the mesentery in a vertical direction and locked (fig. 1 *A*). This causes a shortening of the stomach wall while the jejunum wall remains unaffected. After two such sutures have been done, the soft stomach clamp should be opened temporarily to allow the stomach wall to contract. After the serosa suture along the posterior gastric wall is completed, the jejunum is opened (with as small an opening as possible), and the mucosa-muscularis-serosa suture is carried out. It is a continuous catgut suture, simple along the posterior stomach wall but pleating in along the anterior wall. To take



Fig. 2.—*A*, roentgenogram showing large penetrating ulcer in the proximal third of the lesser curvature, causing hourglass deformity of the stomach. Biopsy revealed a benign lesion. Note the deep crater in the lesser curvature and the approximate line of resection. *B*, roentgenogram taken nine months after resection of four fifths of the stomach. The operation performed was the antecolic Billroth 2 oralis totalis type of resection with pleating in of the stomach. Note the narrowed outlet (*x-x*) above the bottom of the stomach; this causes a valvelike action which prevents the dumping of food. The anastomosis drains well into the efferent jejunal loop.

the knot of this suture away from the corners of the anastomosis, i. e., to take away the weak points from the curvatures, the suture starts from the middle of the posterior wall. It is first led toward the greater curvature, closing this half of the anastomosis. A second suture, also starting from the middle of the posterior wall, closes the other half and meets the first suture in the middle of the anterior wall. When either suture reaches the anterior wall it becomes a pleating-in suture. It is led so that it shortens the anterior stomach wall but not the jejunal wall.

I use the "loop on the mucosa" type of suture. To shorten the gastric wall the loop on the gastric side is made wider than the loop on the jejunal side. Furthermore, the jejunal loops are placed close to each

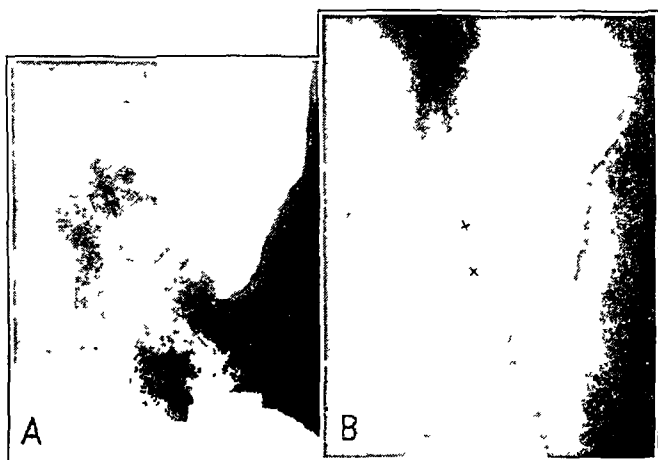


Fig. 3.—*A*, roentgenogram taken four months after resection of the stomach for stenosing pyloric ulcer. The type of resection was the retrocolic Billroth 2 oralis totalis with pleating in of the stomach. Note the restoration of the lift of the stomach achieved by drawing the greater curvature up to the lesser curvature. *B*, roentgenogram taken seven months after gastric resection for duodenal ulcer. The type of resection was the antecolic Billroth 2 oralis totalis with pleating in of the stomach. Valvelike action at the stomach outlet (*x-x*) was obtained, and the anastomosis drains well.

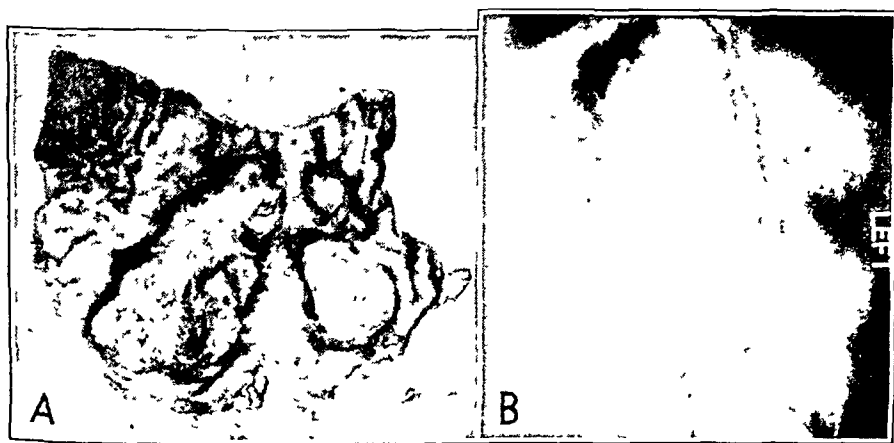


Fig. 4.—*A*, specimen of a gastric resection for Hodgkin's disease of the stomach. *B*, roentgenogram taken four months after resection of three fourths of the stomach. The type of resection was the retrocolic Billroth 2 oralis totalis with pleating in of the stomach.

other. Figure 1 *B* demonstrates this principle better than any description. If necessary, the pleating effect may be increased by leading the loop through the stomach horizontally and through the jejunum ver-

tically. After this suture is completed, the clamp is opened; either a simple interrupted or a continuous Lembert suture approximates the anterior gastric and the jejunal serosa.

This simple pleating-in suture narrows the stomach outlet more than half of its circumference; it attempts to reconstruct the stomach outlet so as to produce as normal anatomic conditions as possible. Owing to the difference in the length of the curvatures, the half toward the lesser curvature is shortened at the expense of the greater curvature, i. e., the greater curvature is drawn up toward the lesser curvature (figs. 2, 3 and 4). Thus the new outlet comes to lie above the axis of the stomach, as the pylorus does in a normal stomach, i. e., the lift of the stomach is restored and a dumping of the food avoided.

I have employed the pleating-in suture in 7 cases in which gastric resection was performed (2 cases of gastric ulcer; 1 of Hodgkin's disease of the stomach, 1 of pyloric ulcer, 1 of gastrojejunal ulcer and 2 of duodenal ulcer). In all cases the functional result was good, as demonstrated symptomatologically and roentgenologically.

SUMMARY

A simple suture for narrowing the stomach outlet in gastric resection of the Billroth 2 oralis totalis type is described. The principle of this suture consists of pleating in the stomach wall.

REVIEW OF UROLOGIC SURGERY

ALBERT J. SCHOLL, M.D.

LOS ANGELES

FRANK HINMAN, M.D.

SAN FRANCISCO

ALEXANDER VON LICHTENBERG, M.D.

MEXICO, MEXICO

ALEXANDER B. HEPLER, M.D.

SEATTLE

ROBERT GUTIERREZ, M.D.

NEW YORK

GERSHOM J. THOMPSON, M.D.

AND

JAMES T. PRIESTLEY, M.D.

ROCHESTER, MINN.

EGON WILDBOLZ, M.D.

BERNE, SWITZERLAND

AND

VINCENT J. O'CONOR, M.D.

CHICAGO

KIDNEY

Resection of the Kidney.—Garcia and Galvez¹ point out that partial nephrectomy is indicated only in those cases in which the remaining portions of the kidney are in sufficiently good condition, both functionally and anatomically, to justify expectation of functional efficiency after this conservative operation. Such cases are relatively few since pathologic processes affecting the kidney usually involve the entire organ. Care must be taken also to ascertain that the blood supply is adequate and that the evacuation of the urine is normal; if these conditions are not fulfilled, operation should not be performed. If these conditions are fulfilled, then after removal of the cause of the lesions, perfect repair and cicatrization of the operative wound are possible, and function of the remaining portion of kidney will be all that can be desired.

Until recently, partial nephrectomy was considered appropriate only in cases of solitary cyst of the kidney, small localized benign tumor, in certain cases of renal trauma and cases of double kidney in which a painful syndrome or pathologic processes affect only one of the excretory

1. Garcia, A. E., and Galvez, I.: La nefrectomia parcial, Rev. argent. de urol. 10:209-234 (March-April) 1941.

systems. Now, however, a new field of usefulness for the procedure has been found, namely, cases of renal lithiasis; in these, cuneiform resection of the kidney at a site corresponding to that of the one or more calices involved may be the operation of choice, since the difficult procedure of extracting fragments of impacted stone is thus avoided.

The technic, which is relatively simple, must face two fundamental problems, namely: (1) The operation must assure the circulation of blood in the organ together with complete hemostasis of the sectioned surface of the parenchyma, and (2) the operation must repair the excretory tract, if this has been compromised by the portion resected, with care not to interfere with emptying. If possible, the larger vessels corresponding to the zone to be resected must be ligated in advance of resection. The sectioned surface must bleed profusely as evidence of the good circulatory condition of the remaining parenchyma except in cases in which the vascular territory is exactly delineated and in which hemorrhage is less profuse.

After the site of section has been chosen, the sectioned surface is made in the shape of a wedge; two flaps are cut in the remaining parenchyma to facilitate, by coaptation, hemostasis and cicatrization. Meticulous hemostasis is basic to the technic. Separate ligature is impossible for arteries of small caliber, and it is necessary to place U-shaped catgut sutures which serve the twofold purpose of stopping bleeding and approximating the edges of the wound. These sutures should be reenforced with perirenal fat (or with the capsule of the organ folded over itself to increase resistance) interposed between the edges of the wound. Other smaller sutures, single or U-shaped, are then placed along the margins.

The second problem, repair of the excretory tract provided it has been involved in the section, is accomplished by separate catgut sutures of the calices or the pelvis at the same time that separate ligation of vessels is carried out. Ligation by temporary compression of the pedicle to produce hemostasis is favored. If resection is performed at the upper pole of the kidney and if it is considered desirable to leave a pelvic drain, a sound may be placed through the open calix, the opening of the calix being reduced with partial suture. Care must be taken not to interfere with the emptying of the organ. This emptying is assured by repair of the pelvic wound, if one exists, freeing the ureter and the pelvis from possible adhesions and fixing the organ in the best position to facilitate the flow of the urine. This nephropexy is accomplished with the capsule; two flaps are cut from what remains of the capsule.

Possible complications are hemorrhage and urinary fistula. The former may be immediate or late; it usually occurs after eight to fifteen days. Late hemorrhage after nephrostomy is usually of grave portent, and, if persistent, secondary nephrectomy will be necessary. Urinary fistula is not likely to appear if there has been no interference with the

excretory apparatus. If a calix or the pelvis has been opened, careful suture will be the best means of avoiding fistula. If one does appear, every effort must be made to find and repair it.

Garcia and Galvez report a case of multiple caliceal lithiasis in a kidney with double pelves and ureters. Partial nephrectomy was indicated for the lower portion of the double organ. The case was complicated by the presence of an anomalous artery at the upper pole; the ligation of this artery apparently was the cause of the urinary fistula which appeared at this site on the eighth day after operation. The fistula discharged urine whenever the patient was recumbent but not when he was in a sitting position. The patient was maintained in the latter position, and the fistula closed on the fiftieth postoperative day. Formation of the fistula was attributed to development of a necrotic region at the point of ligation of the anomalous artery. Although every effort should be made to keep such a vessel intact, there are cases similar to this in which the vessel interferes with the operation. The risk attending ligation must therefore be faced in order to accomplish the purpose of the operation, which, in this case, was saving the upper half of the kidney. The risk, however, is not small, and in less fortunate cases it is possible for results of the operation to be jeopardized.

Yunck and Forsythe² report 19 clinical cases of caliceal resection for stone. In 16 cases, prompt healing and minimal resistant infection occurred, with no recurrence of stone. In the other 3 cases, severe postoperative bleeding was present, and this may have been a factor in producing the poor end results.

The end results of the operation were studied in 13 dogs. In 10, the calix was resected by means of a scalpel with no deaths. Healing was prompt and was complete at the end of fourteen days. Normal parenchyma, in which there was no evidence of ascending infection, was observed within 2 mm. of the operative scar. Although there was microscopic evidence of calcium and formation of bone in the scar was noted in 1 case, in all cases the pelvis was completely reepithelialized, and subepithelial plaques were absent.

In 3 animals, the calix was resected with high frequency cutting current. Two animals died four and five days after operation, respectively. The third animal had marked local sepsis and no evidence of healing.

From these experiments, it appears that resection of the calix with the scalpel is definitely superior to resection with the high frequency cutting current.

Resection of a calix containing stone is indicated because: (1) resistant infection usually is not a factor; (2) healing is prompt, with

2. Yunck, W. P., Jr., and Forsythe, W. E., Jr.: Calyceal Resection: Report of Clinical and Experimental Cases, *J. Urol.* **46**:396-412 (Sept.) 1941.

little danger of permanent urinary fistula; (3) there is little postoperative decrease in function of the kidney, as demonstrated by comparison of the preoperative and postoperative levels of urea and the determinations of phenolsulfonphthalein; (4) in most cases stone does not occur at the operative site or in other calices.

Campbell³ emphasizes the importance of conserving renal tissue in surgical procedures on the kidneys. He states that resections when feasible are being performed more frequently than formerly. He reports the cases of 41 patients who underwent renal resection; there were 2 deaths—a mortality rate of 5 per cent.

Campbell tabulates the indications for resection as follows:

I. Normally formed kidney:

- (a) Localized hydronephrosis due to obstruction of the calices and with or without infection or stone.
- (b) Extension of large pelvic stone into a single calix.
- (c) Solitary cyst or localized multilocular cystic disease.
- (d) Benign neoplasm (rare).
- (e) Certain cases of renal trauma with localized (polar) fragmentation or maceration and the remainder of the organ sound.

II. Anomalous kidney:

- (a) Reduplicated pelvis with one sound pelvoparenchymal segment and the other diseased by hydronephrosis, infection or calculus associated with obstruction (chiefly stricture), infection or an ectopic opening of the corresponding ureter.
- (b) Horseshoe kidney: 1. When the condition itself causes symptoms, chiefly pain, and in the absence of other disease.
2. When the conditions indicated under II a involve half of the horseshoe kidney or, as in 3 of our cases, involve a reduplicated pelvis on one side of a horseshoe kidney.
- (c) Same as II b but for removal of the diseased renal segment in crossed ectopia, sigmoid, L, discoid or other forms of fusion anomaly.

III. In congenital or surgical solitary kidney with a resectable lesion. This includes the clinical equivalent in which the function of the opposite kidney is low (e. g. nephritis or congenital hypoplasia) but its removal is contraindicated.

Resection is not advisable in cases of carbuncle, tuberculosis or neoplasm. Because a large percentage of congenital anomalies are associated with ureteral obstruction and because the condition of the ureter will influence the choice of operation, a good ureterogram is as important as a good pyelogram. Often, the entire ureter draining the diseased renal segment is dilated to the ureterovesical opening, or it is ectopic. Under these circumstances, complete ureterectomy is indicated, and it is advisable to start with removal of the ureter. Whether this is

3. Campbell, M. F.: Resection of the Kidney, J. A. M. A. **117**:1223-1229 (Oct. 11) 1941.

carried out in one or two stages depends on the age and the condition of the patient.

When total ureterectomy is indicated, the following three courses are open:

1. One Stage Ureteroheminephrectomy: For adults in good condition, ureteroheminephrectomy in one stage may be performed. The ureter is first disjoined at its lowermost end through a Gibson or low pararectal incision; it is mobilized as high as possible retroperitoneally and then removed with its attached resected renal segment through the usual loin incision for nephrectomy.

2. Two Stage Ureteroheminephrectomy (Initial Renal Resection): When the condition of the adult patient is less certain, initial renal resection and partial ureterectomy may be performed with subsequent removal of the remaining ureter if the condition of the patient permits. Campbell considers this the best procedure for all children who require total ureterectomy, even for those in good physical condition.

3. Two Stage Ureteroheminephrectomy (Initial Mobilization of the Lower Part of the Ureter and Cutaneous Ureterostomy): When the condition of either the child or the adult patient is poor, and a two stage operation is definitely indicated from the outset, Campbell prefers to begin with an attack on the lower end of the ureter. At the first operation the ureter is disjoined from its point of origin, if ectopic, or from its junction with the bladder if the obstruction is in this region or if the ureter is widely dilated to its termination. The ligated cauterized proximal end is covered by a piece of dam fastened as a hood over the end of the ureter by a tightly tied ligature. The stump of the ureter is mobilized upward as far as possible, usually to the level of the posterior portion of the ilium. The mobilized lower end of the ureter is then brought out through a stab incision 2 or 3 cm. mesial to the level of the iliac crest and anchored to the cutaneous layer with two or three fine sutures. If the cut end of the ureter is turned back on itself in cuff formation for 1.5 or 2 cm. and kept moist for a few days by means of gauze soaked in physiologic solution of sodium chloride, necrosis is not likely to occur. In performing cutaneous ureterostomy in this manner it is good practice to fasten indwelling in the ureter a large four eye Robinson type catheter, which will facilitate healing of the wound by drainage of the infected urine to an appropriate receptacle. Later, when the condition of the patient permits, the kidney is exposed and the upper portion of the ureter is mobilized down to the point of cutaneous ureterostomy, which, by a racquet-shaped continuation of the loin kidney wound, is excised completely. The lower portion of the ureter and the stump left after ureterostomy are wrapped in a protective pad, and renal resection is carried out, the diseased tract being entirely removed.

Postoperative infection of wounds and renal necrosis caused by thrombosis and ischemia are the most frequent complications. Campbell has placed powdered sulfanilamide into contaminated wounds, using as much as 8 Gm. in the wounds of older children, with encouraging results.

Surgical Technic.—Digby¹ discusses an approach to the kidney by an incision over the twelfth rib. An incision is made directly over the twelfth rib; the rib is resected, and the periosteum above the subcostal vessels is incised. He claims that this gives much freer exposure to the kidney and avoids damage to the subcostal vessels and nerves and their branches. Injury to the pleura can be avoided by study of roentgenograms of the lower limit of the pleura before operation and by exposing the outer edge of the rib before incising it prior to resection. Digby carried out this incision in 13 cases without accident and states that this incision gave him free exposure in all cases.

Barnes and Bergman² discuss transperitoneal nephrectomy and report 17 cases in which this procedure was carried out.

To expose the kidney, the abdomen is opened by a longitudinal midrectus or pararectus incision; from this, a transverse incision is carried laterally over the mass of the tumor. The intestines are then displaced medially and retained by means of a large warm pack. The posterior peritoneal layer is incised laterally to the ascending or descending part of the colon. The ureter and the renal pedicle usually are readily identified; this facilitates their clamping and ligation under direct vision. In cases of malignant disease, the pedicle should be clamped as early as possible to prevent dissemination of tumor cells into the circulation. A greatly enlarged kidney may encroach on the inferior vena cava or the aorta to such an extent that it is difficult to separate the kidney from these large vessels. The inferior vena cava is easily injured, and its thin wall may be perforated while freeing adhesions between it and the enlarged kidney. When such an injury occurs while operating through a lumbar approach, it is difficult to control bleeding from the rent in the vena cava. The transperitoneal approach, however, gives adequate exposure so that an injury to the vena cava is easily seen and hemorrhage can be temporarily controlled by means of pressure. In Barnes and Bergman's series, injury to the vena cava occurred in 4 cases. In 2 of these, a clamp was applied and left in place; it was removed between the tenth and fourteenth postoperative days. In 2 other cases, the rent was sutured with fine catgut after clamping the vena cava. After removal of the mass, it is better to drain the

4. Digby, K. H.: The Twelfth Rib Incision as an Approach to the Kidney, *Surg., Gynec. & Obst.* **73**:84-85 (July) 1941.

5. Barnes, R. W., and Bergman, R. T.: Transperitoneal Nephrectomy, *J. Urol.* **46**:545-548 (Sept.) 1941.

retroperitoneal space through a stab wound in the lumbar region, although some surgeons prefer to close the renal fossa without drainage. The posterior and then the anterior layer of peritoneum are sutured with continuous catgut. The abdomen is closed without drains. A mattress suture is used to approximate the cut ends of the rectus muscle; the fascia is brought together with chromic forty day no. 1 catgut in a running suture, and the skin is approximated in the usual manner.

After removal of large renal neoplasms, the ultimate prognosis is poor. When operation results in a prolongation of normal life and activity for a year or more, Barnes and Bergman feel that the temporary relief given the patient by removing the large mass is worth the risk and the inconvenience of the operation.

Anomaly.—Woodruff⁶ reports a case of triplication of the ureter and the renal pelvis. The patient, a man aged 74 years, was originally examined because of symptoms caused by an enlarged prostate. Cystoscopy revealed three normal-appearing renal orifices on the right side and one on the left. All three orifices were catheterized. A pyelogram revealed triplication of the renal pelvis.

Mallard⁷ states that renal hypoplasia is essentially a diminutive normal kidney but that it is more subject to infection. The characteristic symptom of this type of kidney is pain. This pain is not due to the kidney being diminutive but is due to concurrent changes. There are no characteristic symptoms of hypoplastic kidney.

Renal hypoplasia of itself will not cause cardiovascular hypertension.

The diagnosis is made essentially by the characteristic pyelograms and the kidney shadow as seen roentgenographically. Usually, the upper calix is long; this particular calix and the pelvis of the kidney are in a straight line with the ureter.

The treatment for this type of kidney should be about the same as the treatment for a kidney of normal size. However, as a kidney of this sort has little function, nephrectomy is indicated more readily than for the normal kidneys under similar conditions.

Mallard reports 4 cases of congenital hypoplasia of the kidney. In 2, nephrectomy was performed because of infection.

Burt, Lane and Hamilton⁸ report a case in which a triple kidney and three complete ureters were present on the right side; one ureter had an extravesical opening. There was a double kidney with a Y-shaped ureter on the left side. This is a rare anomaly, since a review

6. Woodruff, S. R.: Complete Unilateral Triplication of the Ureter and Renal Pelvis, *J. Urol.* **46**:376-379 (Sept.) 1941.

7. Mallard, R. S.: Congenital Renal Hypoplasia: Report of Cases, *J. Urol.* **46**:216-234 (Aug.) 1941.

8. Burt, J. C.; Lane, C. M., and Hamilton, J. L.: An Unusual Anomaly of the Upper Urinary Tract, *J. Urol.* **46**:235-240 (Aug.) 1941.

of the literature failed to disclose a report of any similar case. Lau and Henline reported a case of three complete ureters on the right side with three openings into the bladder. Their case was the only authentic one reported since their search of the literature revealed only 7 cases in which three or more ureters were present on one side; in each of these, however, evidence was insufficient to give complete proof of the existence of the ureters.

Fowler⁹ states that 36 cases of bilateral renal ectopy have been reported in the literature. To these he adds 4 cases, making 40 to date. Of these, 22 were encountered clinically and 18 at necropsy.

These kidneys function normally and are not incompatible with health. Since the condition is not productive of symptoms, it frequently is unrecognized.

The lesions complicating bilateral ectopic kidneys are those commonly encountered in normally placed organs. The symptoms produced by complications are atypical, confusing and frequently misinterpreted. The preoperative diagnosis can be made only by routine urologic study, including intravenous and retrograde pyelography.

Treatment, when necessary, is similar to that employed for kidneys in normal position.

Stone.—Rupel and Brown¹⁰ report a case in which nephrostomy with removal of the renal stone was carried out. Cystoscopic examination disclosed that only the left kidney was functioning. The right kidney was large, and the pelvis was filled with many stones. Nephrectomy was performed on the right side. Later, it was observed that the opposite kidney was obstructed by a stone lodged at the ureteral pelvic juncture. Nephrostomy was carried out; after this the patient's general condition improved. A panendoscope was inserted into the kidney through the nephrostomy opening. The renal pelvis was dilated with water, and the stone was seen, grasped and removed with the instrument. The patient showed a good operative result.

Ezickson and Morrison¹¹ discuss the role of the liver and the thyroid gland in the production of renal calculi. Studies were carried out to determine the incidence of hepatic dysfunction in an unselected group of patients who had had urinary lithiasis or had it at the time of the studies. They incorporated likewise studies pertaining to the basal metabolic rate and cholesterol determinations.

9. Fowler, H. A.: Bilateral Renal Ectopia: A Report of Four Additional Cases, *J. Urol.* **45**:795-812 (June) 1941.

10. Rupel, E., and Brown, R.: Nephroscopy with Removal of Stone Following Nephrostomy for Obstructive Calculous Anuria, *J. Urol.* **46**:177-182 (Aug.) 1941.

11. Ezickson, W. J., and Morrison, L. M.: The Role of the Liver and Thyroid as Metabolic Factors in the Production of Renal Calculi, *J. Urol.* **46**:359-375 (Sept.) 1941.

Function of the liver was ascertained by estimation of the concentration of bile salts in the hepatic bile.

Twenty of the patients (34 per cent) revealed evidence of hepatic dysfunction. Of this group, 11 (61 per cent) had an abnormal basal metabolic rate, and 12 (50 per cent) had hypercholesteremia.

Of 17 patients with active urinary symptoms at the time the studies were made, 10 (59 per cent) had hepatic dysfunction. This was in contrast to the 42 patients without active urinary symptoms, 10 (24 per cent) of whom had hepatic dysfunction. These studies seem to reveal a definite relation between hepatic dysfunction, abnormal basal metabolic rate and hypercholesteremia.

Analysis of the results of these studies reveals that hepatic dysfunction is frequently associated with urolithiasis. The significance of this relation remains to be determined, but it seems that some disturbance in metabolism, in which both the liver and the thyroid gland play a part, is concerned with the development of certain types of urinary stones.

Lindahl and Bargaen¹² state that renal calculi occur more frequently among patients suffering from chronic ulcerative colitis who undergo ileostomy in which the colon is not afterward removed than they do among patients suffering from chronic ulcerative colitis who do not undergo ileostomy. The basis for the formation of renal calculi might be the infected portion of the remaining part of the colon. Two of the many complications of chronic ulcerative colitis for which ileostomy has been performed without subsequent removal of the colon appear to be renal calculi and infection of the urinary tract. It does not seem likely that change in the metabolism of calcium and phosphorus occurs as the result of exclusion of the colon by ileostomy. The study of the authors seems to emphasize further the fact that ileostomy does not cure chronic ulcerative colitis and that complications continue to occur after performance of ileostomy that appear to be secondary to the infection still present in the remaining portion of the colon.

Boyd¹³ states that recognition of the existence and the causes for the formation of renal calculus in cases of poliomyelitis is a matter of great importance. Most patients with poliomyelitis have had a sufficient loss of sensation to exclude or mask the symptoms ordinarily produced by renal or ureteral calculi. Time and again, cases of extensive formation of stone in the kidneys and even in the ureters occur with so little symptomatic evidence of the presence of the condition that no suspicion of the trouble exists until the disease is far advanced. Urinary infections are common in a large percentage of the cases of poliomyelitis in

12. Lindahl, W. W., and Bargaen, J. A.: Nephrolithiasis Complicating Chronic Ulcerative Colitis After Ileostomy: A Report of Six Cases, *J. Urol.* **46**:183-192 (Aug.) 1941.

13. Boyd, M. L.: The Significance of Sensory Paralysis in Poliomyelitis Patients in Whom Renal Calculi Develop, *J. Urol.* **45**:647-651 (May) 1941.

which paralysis is sufficient to cause the patients to be bedridden for several months.

Urinary infection is usually blamed for the fever which appears when the stones begin to cause urinary obstruction, because there is so little pain; medicines are prescribed when roentgenograms and a complete urologic examination should be made.

Boyd reports the case of a boy who had the best medical attention and advice and yet when seen was in great trouble with severe chronic pyelonephritis on the left and a stone completely blocking the left ureter. The boy showed the effects of long-standing infection plus symptoms of high retention of nitrogen. Because of partial paralysis, the usual symptoms of obstruction from ureteral stone were absent. Recovery followed removal of the stone.

Boyd states that when infections of the urinary tract occur, they should be treated by urinary antiseptics and that some adequate measure should be employed for relief of the injurious effects which result from residual urine, whether intermittent catheterization or suprapubic cystotomy. A retention catheter almost always produces prostatitis, seminal vesiculitis and, eventually, epididymitis.

A suitable diet to maintain acidity of the urine is important. Citrus fruit juice should be given in moderation but not at all if the urine is alkaline or faintly acid. Alkaline drugs, such as milk of magnesia, sodium bicarbonate or saline laxatives containing alkalis, should not be given. An adequate intake of fluid should be maintained to prevent the urine from becoming concentrated. The patient's position should be changed frequently and as completely as possible, and he should lie on the abdomen an hour or two at a time every day as soon as the paralysis and general condition will permit.

Routine roentgenograms should be made at given intervals, and a complete urologic examination should be carried out if there is the least suspicion that the kidneys are infected or that a deposit of urinary salts in the urinary tract is taking place.

Calcium Plaques.—Vermooten¹⁴ stated that the deposition of calcium in the renal papilla occurs among South African (Bantu) Negroes in a form indistinguishable from that occurring among Caucasians. The incidence, however, is much lower.

Although calcium plaques have been encountered among patients less than 20 and more than 80 years of age, there is a marked increase in incidence between the ages of 50 and 80 years; this indicates that age and its associated physiologic changes are important factors in causing this condition. The incidence is twice as great among men as it is among women.

14. Vermooten, V.: The Incidence and Significance of the Deposition of Calcium Plaques in the Renal Papilla as Observed in the Caucasian and Negro (Bantu) Population in South Africa, *J. Urol.* **46**:193-200 (Aug.) 1941.

If patients who have cardiac disease and arteriosclerosis are excluded, calcium plaques are present among as many apparently healthy persons as among hospital patients. The precipitation of urinary salts on the calcium plaque must have a dietary or a metabolic controlling factor, for, although among South African Negroes the plaques form, renal calculi are not deposited on these plaques. The deposition of calcium in the renal papilla appears to be a change involving the collagen fibers in the renal papilla as a whole and is not limited to those fibers which surround the tubule.

Tuberculoma.—Bugbee¹⁵ reports tuberculoma of the kidney of a woman 30 years of age. Cystoscopy revealed regions of congestion throughout the bladder. It was found that the left ureter was displaced laterally and that the vesical urine contained tubercle bacilli. A urogram of the left kidney disclosed a definite filling defect suggestive of a tumor of the renal pelvis. The kidney was removed and split throughout its length; the pelvis was found to be filled with a smooth pinkish mass which had the appearance of a renal tumor. Microscopic examination revealed that the original diagnosis of tuberculosis was correct.

In this case an early stage of the disease was represented in which the tuberculous process presents a definite tumor formation. Necrosis and formation of a cavity had not taken place. Although definite hemorrhagic regions were present in the bladder, the ureter apparently was not involved.

Polycystic Kidneys.—Norris and Herman¹⁶ discuss theories of the origin of polycystic kidneys and describe 4 cases of congenital renal polycystic disease.

Evidence has been given that for a long period in fetal life development of the kidneys is normal. Focal cystic dilations of uriniferous tubules and collecting ducts occurring after differentiation of the metanephrogenic anlage and after the union of the elements with collecting ducts are followed by isolation as cysts of segments of these nephrons. Anastomosis among these cysts results from continued proliferation of these elements and from rupture of their walls. These changes are thought to be degenerative, since they resemble the stages in the normal degeneration of the mesonephros and of normally vestigial elements of the metanephros. In polycystic kidneys, therefore, the metanephros is abnormally provisional to a variable degree. Such an explanation appears to be applicable to most of the congenital anomalies associated with polycystic kidneys and to be compatible with the hereditary nature

15. Bugbee, H. G.: Tuberculoma of the Kidney: Report of a Case, *J. Urol.* **46**:355-358 (Sept.) 1941.

16. Norris, R. F., and Herman, L.: The Pathogenesis of Polycystic Kidneys: Reconstruction of Cystic Elements in Four Cases, *J. Urol.* **46**:147-176 (Aug.) 1941.

of the disease. The fundamental cause of polycystic disease of the kidneys must be in the germ plasm.

Lipoma.—Robertson and Hand¹⁷ report 2 cases of primary intrarenal lipoma and discuss 12 cases reported in the literature in which the lipoma was removed surgically. Tumors of this type, because of their cortical and subcortical positions in the kidney, may attain considerable size before giving rise to symptoms. Pain and hematuria may call attention to the presence of such a tumor at an early date. Clinically, primary renal lipoma may be indistinct from primary renal carcinoma. Intrarenal lipoma may contain variable amounts of connective tissue, smooth muscle, myxomatous vascular tissue and cartilage, or it may reveal sarcomatous transformation.

A new concept of the origin of primary intrarenal lipoma is suggested, namely, that it arises from the embryonic connective tissue surrounding the developing collecting tubules. The embryonic connective tissues may be pushed to a cortical or a subcapsular position by the developing buds of the collecting tubules.

Rupture.—Williams¹⁸ reports a case of subcapsular rupture of the kidney. The patient was a woman aged 31 years who had been injured in an automobile accident. Shortly after the accident hematuria occurred. On examination, abrasions were found over the right lower ribs and the right iliac crest. The right loin was tender and swollen, and the lower pole of the right kidney was enlarged. On the fifth day after injury, roentgenograms revealed an increase in the right renal outline. An excretory urogram did not disclose any abnormalities on the left side; on the right, the excretory return of the upper calices was normal, but the lower calices could not be defined. A vague opacity was noted in the region of the lower pole of the right kidney. A right retrograde pyelogram was then made, and the contrast medium was seen to pass out from two ruptured calices at the lower pole to collect in a puddle below the kidney. Williams expresses the opinion that a subcapsular rupture of two calices was present with the contrast medium freely entering the space caused by the stripping of the true renal capsule by blood and urine.

Perirenal Abscess.—Kindall¹⁹ reports a case of perirenal abscess with the formation of gas and multiple metastatic abscesses of the lung caused by Friedländer's bacillus (*Klebsiella pneumoniae*). The patient was a man aged 63 years. This case is unique in that no similar one

17. Robertson, T. D., and Hand, J. R.: Primary Intrarenal Lipoma of Surgical Significance, *J. Urol.* **46**:458-474 (Sept.) 1941.

18. Williams, E. R.: Subcapsular Rupture of the Kidney: Case Report, *Brit. J. Radiol.* **14**:248-249 (July) 1941.

19. Kindall, L.: Perirenal Abscess with Gas Formation and Metastatic Pulmonary Abscesses Due to Friedlaender's Bacillus: A Case Report, *J. Urol.* **46**:555-561 (Sept.) 1941.

has been found in the literature. Incision and drainage of the perirenal abscess were followed by satisfactory recovery. The source of the bacillus in this case was not known. The pyelograms were normal, and repeated cultures of the urine failed to yield the causative organism.

In a review of the literature, Kindall found that Friedländer's bacillus is present in almost every organ of the body, most frequently in the gastrointestinal tract and next frequently in the genitourinary tract; involvement of the lungs is rare.

Moore²⁰ has studied 50 cases of juxtarenal infection. Anatomically, he classifies 47 as perinephric and 3 as paranephric. Inflammation of the perinephrium may result from hematogenic infection or from direct spread from renal disease. These primary and secondary types differ fundamentally. In the primary type, the manifestations of the perinephric infection form the whole clinical and pathologic picture. Symptoms, signs or residual evidences of renal disease are not evident. Moore's observations lead him to agree with Vermooten that the common mechanism in cases of so-called primary perinephric abscess is infection from the blood stream, although he does not deny that in rare cases the perinephric tissue is infected from gross renal suppuration, such as carbuncle. In a great majority of cases, the bacteremia responsible for infection of the perinephric fat results from sepsis of the skin. Occasionally it is derived from infected abrasions, wounds or respiratory disease. Of the 50 cases studied, 37 were cases of primary perinephric infection. A history of previous boils or carbuncles was elicited in 10 cases. In 6 cases, some other infective lesion had been present, such as mastoiditis, coryza, infected sacral dermoid or influenza. The shortest interval noticed in these cases was four weeks and the longest one year. In 2 cases, trauma was known to be responsible for localization of the infection in the perinephrium. *Staphylococcus aureus* was the infecting organism in 73 per cent of the cases in which cultures were made. In 3 cases, *Staphylococcus albus* was responsible, and in 2, hemolytic streptococcus also was found. It may therefore be concluded that in most cases the predisposing lesion had been a staphylococcic infection of the skin. It is well to remember that suppuration by no means occurs in all cases. In some the perinephrium becomes thickened and inflamed without the formation of pus. The kidney is usually entirely normal. In rare cases, the abscess may spread across the midline and affect the other side.

The most striking feature about perinephric infection is the silence. The onset is insidious, and it may be days or weeks before local pain is experienced. This is usually felt in the loin and may become worse on deep breathing. The most important clinical findings are a tender fixed renal swelling with the usual general signs of infection, such as tachycardia, pyrexia or leukocytosis. Urinary symptoms do not appear,

20. Moore, T.: Juxtarenal Infections, *Brit. J. Urol.* **13**:1-7 (March) 1941.

and the urine is normal. Intravenous urography is sometimes useful in disclosing a deformity of the renal pelvis due to pressure of the abscess. Another important point is limitation of the normal respiratory excursions of the kidney. As diagnosis is likely to be delayed, patients are late in receiving correct treatment. The prognosis, however, is good, as drainage of the perinephric tissues alone suffices in most cases.

Secondary perinephric infections are those which arise from renal disease. The commonest are calculous disease (present in 7 of 10 cases in this series); others are noncalculous pyonephrosis, ascending pyelonephritis and renal carbuncle. Six patients were men, and 4 were women. The right side was affected in 4 cases, the left in 6. Treatment consists of correction of the underlying renal disorder, either before or after drainage of the abscess; thus the prognosis is poorer.

Paranephric infection is rarely primary and was present in only 1 case in this series. It is distinguished from perinephric infections by the fact that it lies outside the fascia of Gerota. The secondary infection reaches the paranephrium from contiguous structures, usually the colon. Two of the author's 50 cases were in this class. One was attributable to perforation of the colon by a fishbone and the second to carcinoma of the colon. Both infections proved fatal. In addition to signs of the underlying disease, there was evidence in these cases of general infection, together with local manifestations of inflammation in the nature of tenderness, and later, a mass. The exact situation of the lesion can be demonstrated only by careful investigation, including pyelography and enemas of barium sulfate, and often only by surgical exploration. Owing to the nature of the underlying disease and of the organisms concerned, which are derived from the colon, it can be readily understood that recovery is uncommon.

Atcheson²¹ states that perinephric abscess may present a variety of clinical pictures and that it should always be considered as a possibility in cases of prolonged fever. In most cases, a pyogenic lesion occurs in the renal parenchyma before the perirenal space is involved. Secondary involvement of the perinephric space may occur by direct rupture of the abscess or may follow the veins and the lymphatics between the kidney and the perinephric space.

Two main groups of lesions precede the renal lesion, namely, (1) distant foci of infection, such as furuncles, and (2) chronic diseases of the kidney itself, such as calculi or pyonephrosis. The abscesses occur most commonly among men between the ages of 25 and 45 years. The onset is usually prolonged, and the diagnosis is seldom made before the patient has had symptoms for five or six weeks. Roentgenograms are becoming more important in diagnosis, but too much emphasis should not be placed on negative roentgenograms.

21. Atcheson, D. W.: Perinephric Abscess with a Review of One Hundred and Seventeen Cases, *J. Urol.* **46**:201-208 (Aug.) 1941.

Practically all patients have pain, costovertebral tenderness, fever and leukocytosis. In a great many cases, however, some of the commonly stressed findings, such as spasm of the psoas muscle, flexion of the hip and changes in the urine, are absent. The postoperative course is prolonged and coupled with a high mortality rate.

The only treatment is incision and drainage with postoperative supportive measures. It is best not to close the wound too tightly, and in certain types of cases, a counterincision in the wall of the lower portion of the abdomen will facilitate recovery.

Pyelonephritis.—Hyams and Kenyon²² present the clinical and pyelographic features of the early, intermediate and terminal stages of what they term "localized obliterating pyelonephritis" and stress the possibility of the development of these signs in the course of pyelonephritis and calculus disease. They express the belief that many patients who have pyelonephritis are not examined completely. Manifestly normal urograms and negative cultures do not necessarily insure complete arrest of the inflammatory process. Satisfactory diagnostic data can be obtained only by means of complete ureteropyelograms with occlusion catheters, and in the presence of the slightest suggestive change these studies should be repeated at suitable intervals over a long period. In certain cases in which an early tendency toward obliteration is recognized, eventual scarring and contraction may develop despite chemotherapy and local instrumental treatment.

When advanced or terminal changes have supervened, partial nephrectomy should be considered in instances in which the process is definitely limited to a suitable portion of the kidney. It seems that the intensive treatment of pyelonephritis prior to the occurrence of peripelvic extension is the most logical prophylactic measure.

Hypertension.—Riggs and Satterthwaite²³ report an unusual anomaly, a single kidney and ureter on the right side with obstruction of the renal artery by a small dissecting aneurysm and a localized sclerotic plaque in a case of hypertension. The development of hypertension in the acute phase in this case may have been initiated by partial occlusion of the lumen and the three branches of the main renal artery by the aneurysm. Riggs and Satterthwaite state that hypertension, especially that which is sudden in onset, no matter what the age of the patient, appears to warrant complete investigation of the renal arteries for abnormalities.

22. Hyams, J. A., and Kenyon, H. R.: Localized Obliterating Pyelonephritis, *J. Urol.* **46**:380-395 (Sept.) 1941.

23. Riggs, T. F., and Satterthwaite, R. W.: Unilateral Kidney with Partial Occlusion of the Renal Artery Associated with Hypertension: Case Report, *J. Urol.* **45**:513-518 (April) 1941.

News and Comment

American Association of Industrial Physicians and Surgeons and American Industrial Hygiene Association.—The American Association of Industrial Physicians and Surgeons and the American Industrial Hygiene Association will hold their joint annual convention in Cincinnati April 13 to 17, 1942. Medical and hygienic problems associated with the present huge task of American industry will be presented and discussed in clinics, lectures, symposiums and scientific exhibits. The meeting will provide a five day institute for the interchange and dissemination of information on new problems, as well as for the consideration of up-to-date methods of dealing with those that are well known. The industrial physicians have taken responsibility for the program of the first two and one-half days and the hygienists for that of the remaining two and one-half days, but most of the subjects chosen for discussion will be of interest not only to physicians but to industrial engineers and executives.

PHYSIOLOGY OF GASTRIC SECRETION, PARTICULARLY AS RELATED TO THE ULCER PROBLEM

M. J. SCHIFFRIN, PH.D.

AND

A. C. IVY, M.D., PH.D.

CHICAGO

The purpose of this paper is to present a brief review of certain aspects of the physiology of gastric secretion with the idea of indicating their actual or possible relation to the ulcer problem. No attempt will be made to list and evaluate the numerous theories of the genesis of ulcer.

The matter will be divided into three main sections. The first will deal with the normal physiology of stimulation and inhibition of gastric secretion and its composition and will contain a note regarding the normal control of gastric acidity. The second will deal with the abnormal factors which influence gastric secretion. The third will deal with gastric secretion as affected by ulcer and the relation of gastric juice to the causation of ulcer.

I. THE NORMAL PHYSIOLOGY OF GASTRIC SECRETION

The Interdigestive or Continuous Secretion, or the Interdigestive Period of Secretion.—The empty or fasting stomach usually secretes a small amount of gastric juice which is referred to as the interdigestive or continuous secretion. The normal rate of this secretion in man has been reported to be between 30 to 60 cc. per hour¹ and 15 to 117 cc. per hour.² Pavlov³ denied the existence of continuous secretion and attributed such secretion as took place to psychic factors. It is difficult to deny this criticism absolutely; however, interdigestive secretion is known to occur in fasting with vagotomized pouches. Although the mechanisms concerned in its stimulation are obscure, its existence cannot be ignored.

From the Department of Physiology and Pharmacology, Northwestern University Medical School.

1. Ivy, A. C.: *Surgery* 10:861, 1941.

2. Ihre, B.: *Acta med. Scandinav.*, 1938, supp. 95, p. 1.

3. Pavlov, I. P.: *The Work of the Digestive Glands*, translated by W. H. Thompson, London, C. Griffin & Co., 1910.

There is some evidence that the mechanism of the interdigestive secretion may be disturbed in the patient with ulcer and may assume major proportions; this will be discussed later. Atropine, which normally abolishes this secretion, is not so effective in the presence of clinical and experimental ulcer.⁴ On this basis, it has been suggested that irritated mucosa, like other irritated tissues (e. g., skin), produces histamine, since a histamine stimulus is the only one known which is not completely abolished by ordinary doses of atropine.¹

The Gastric Secretory Response to a Meal—The Digestive Secretion—The Digestive Period of Secretion.—The digestive period of secretion is conveniently divided into three phases: the cephalic, the gastric and the intestinal. Each phase denotes the region in which the stimuli are acting to excite gastric secretion.

The cephalic phase is provoked by stimuli such as the thought, smell, sight or taste of food. These stimuli act in the presence of appetite through either conditioned (learned) or unconditioned (unlearned) reflexes. The vagi are the efferent nerves of the cephalic phase, since section of these nerves will abolish this phase of secretion; this phase can be abolished also by atropine. The gastric juice of the cephalic phase is highly acid and possesses considerable peptic activity. The amount of juice secreted during the cephalic phase in man is extremely variable, and its importance in the causation of ulcer is uncertain. This is due to several factors. First, the volume of secretion is affected by the appetite, the attitude of the subject, the type of food (agreeable or disagreeable), the time consumed in its ingestion, especially in the process of mastication, and the manner in which the food is prepared. Second, there is a lack of uniformity in the methods used by various investigators. No method of stimulating the cephalic phase or of determining the peptic activity of the juice has been generally accepted and employed. Since the cephalic phase is mediated by the vagi, it may be that the intravenous administration of insulin would give the most reproducible data for estimating the secretory potentiality of the vagi. Insulin provokes gastric secretion by the hypoglycemic stimulation of the vagal center. Ihre² made extensive use of this method and obtained about 140 cc. per hour from normal men. The cephalic phase, when studied by other methods, has given values of 50 to 150 cc. in twenty minutes.¹ Babkin⁵ properly emphasized that the cephalic phase of secretion and the possibility that it may be exaggerated must not be neglected in any consideration dealing with the applied physiology of gastric secretion.

The gastric phase of secretion can be stimulated by mechanical distention and secretagogues. The secretagogues may be naturally

4. Keefer, C. S., and Bloomfield, A. L.: Effect of Atropine on Gastric Function in Man: Quantitative Study, *Arch. Int. Med.* **38**:303 (Sept.) 1926. Ivy.¹

5. Babkin, B. P.: *Canad. M. A. J.* **38**:421, 1938.

present in the food or may arise as products of the digestion of food. Secretagogues may act per se or through the liberation of a gastric hormone. The exact mechanism of this stimulation of gastric secretion is uncertain. The vagi (preganglionic fibers) are not necessary for this phase of secretion. There are no satisfactory data regarding the volume of the gastric phase of secretion in man. The gastric phase of secretion will vary according to the time the food remains in the stomach, and this phase is still further complicated in the normal man by regurgitation and the overlapping of the intestinal and gastric phases of secretion. A more detailed review of this phase of gastric secretion may be found elsewhere.⁶

The intestinal phase of gastric secretion is provoked by the presence of secretagogues in the intestine. Mild distention of the intestine is without effect, and more serious distention inhibits gastric secretion. However, if the intestinal mucosa is injured, the release of histamine may stimulate gastric secretion. There are no data on the intestinal phase of gastric secretion in normal men. Garbat⁷ obtained values of 120 to 170 cc. in two hours in patients with moderate gastric disorders.

The total volume of gastric secretion has been estimated at 2 to 3 liters per day,⁸ but again there are no methods which give us exact data on man. The total volume of secretion is affected by the type of food ingested; for example, pure carbohydrates are much less potent stimuli than protein in the form of meat. Babkin⁹ reviewed the literature dealing with the comparative potency of various foods as stimuli of gastric secretion.

The Inhibition of Gastric Secretion.—Two types of mechanisms are concerned in the normal inhibition of gastric secretion. First, there is nervous inhibition; both the vagi and the splanchnic nerves contain inhibitory fibers, and mental states may inhibit gastric secretion through these pathways. Distention of the intestine also inhibits gastric secretion, and this may take place reflexly. The second is humoral inhibition, in which the hormone enterogastrone is concerned. The normal mechanism for the release of enterogastrone is the presence of fat in the intestine. This hormone has been purified so that it may be administered intravenously or subcutaneously to dogs. It inhibits gastric secretion and motility.¹⁰ Enterogastrone has been effective in preventing

6. Babkin, B. P.: *Am. J. Digest. Dis.* **1**:715, 1934. Necheles, H., in Portis, S. A.: *Diseases of the Digestive System*, Philadelphia, Lea & Febiger, 1941, p. 84. Ivy.¹

7. Garbat, A. L.: *Tr. Am. Gastro-Enterol. A.*, 1923, p. 45.

8. Rowntree, L. G.: *Physiol. Rev.* **2**:116, 1922.

9. Babkin, B. P.: *Physiol. Rev.* **8**:365, 1928.

10. Gray, J. S.; Bradley, W. B., and Ivy, A. C.: *Am. J. Physiol.* **118**:463, 1937.

the production of experimental gastrojejunal ulceration.¹¹ An effort to further purify the agent or agents responsible so that its use in man will be possible is at present being made.

Acid Inhibition.—Under certain conditions, acid (0.2 to 0.4 per cent) in the stomach or the duodenum inhibits gastric secretion. It is effective in the stomach in the presence of the gastric phase of secretion but not in the presence of the intestinal phase. Acid in the intestine inhibits the action of secretagogues in both the stomach and the intestine. If the stimulus for gastric secretion is sufficiently strong, acid will be ineffective. Acid inhibition fails also in the presence of the cephalic phase of secretion.¹² The inhibitory effects of acid appear to be due to a nervous rather than a humoral mechanism.

Substances in the Urine Which Affect the Stomach.—Sandweiss, Saltzstein and Farbman¹³ were able to delay or prevent the production of experimental ulcer in dogs by the administration of extracts of human pregnancy urine and normal female urine. Further investigation of urinary extracts resulted in a preparation which inhibits gastric secretion and is free of pyrogenic impurities¹⁴ and gonadotropic hormones.¹⁵ The active principle which inhibits the secretion of acid was given the name urogastrone¹⁴ to distinguish it from enterogastrone. Some evidence¹⁶ has been obtained which indicates that the two substances (urogastrone and the substance of Sandweiss and associates) are not identical. It does not seem likely that urogastrone in its present state of purification would have much immediate practical value in the treatment of ulcer in man because of the large quantities of urine necessary for its manufacture. An attempt to evaluate urogastrone in the clinical treatment of ulcer will probably have to wait until the active principle has been isolated and chemically synthesized in large amounts. It is

11. Hands, A. P.; Fauley, G. B.; Greengard, H., and Ivy, A. C.: *Am. J. Physiol.* **133**:P126, 1941.

12. Day, J. J., and Webster, D. R.: *Am. J. Digest. Dis.* **2**:527, 1935. Thomas, J. E.; Crider, J. O., and Mogan, C. O.: *Am. J. Physiol.* **108**:683, 1934. Wilhelmj, C. M.; McCarthy, H. H., and Hill, F. C.: *ibid.* **120**:619, 1937. Wilhelmj, C. M.; O'Brien, F. T., and Hill, F. C.: *ibid.* **115**:429, 1936.

13. Sandweiss, D. J.; Saltzstein, H. C., and Farbman, A.: *Am. J. Digest. Dis.* **5**:24, 1938; **6**:16, 1939.

14. Gray, J. S.; Culmer, C. U.; Wieczorowski, E., and Adkison, J. L.: *Proc. Soc. Exper. Biol. & Med.* **43**:225, 1940.

15. Culmer, C. U.; Atkinson, A. J., and Ivy, A. C.: *Endocrinology* **24**:631, 1939. Friedman, M. H. F.; Recknagel, R. O.; Sandweiss, D. J., and Patterson, T. L.: *Proc. Soc. Exper. Biol. & Med.* **41**:509, 1939. Gray, J. S.; Wieczorowski, E., and Ivy, A. C.: *Science* **89**:489, 1939.

16. Friedman, M. H. F.; Saltzstein, N. C., and Farbman, A.: *Proc. Soc. Exper. Biol. & Med.* **43**:181, 1940. Sandweiss, D. J., and Friedman, M. H. F.: *Am. J. Digest. Dis.* **7**:50, 1940. Wieczorowski, E.; Gray, J. S.; Culmer, C. U., and Wells, J. A.: *Am. J. Physiol.* **133**:P490, 1941.

not known what role, if any, urogastrone plays in the normal regulation of gastric secretion.

The Regulation of the Acidity of the Gastric Contents and Digestion.—The aforementioned factors play a role in the stimulation and inhibition of the volume output of secretion. The volume output of secretion and the rate of gastric evacuation are obviously concerned in the regulation of gastric acidity and digestion; in fact, we mention the point because these factors are frequently omitted from discussions of the regulation of the acidity of the gastric contents. It should be clear that as digestion proceeds, the stimulating effect of the food declines and the volume of secretion is accordingly diminished. Shortly after the meal has been ingested, the cephalic phase declines. Then, as the stomach empties, the gastric phase declines, and the secretagogues acting in the intestine are digested and absorbed. This is the chief cause of the rise and fall in the volume of secretion. Of course, such factors as enterogastrone, gastric emptying time and acid inhibition contribute to modify the character of the curve both qualitatively and quantitatively.

Factors other than the volume of gastric secretion and gastric evacuation operate to regulate the acidity of the gastric contents and its proteolytic activity. Three factors are chiefly concerned: 1. Food combines with, or "buffers," acid and pepsin; this in part explains the relief food affords to patients with ulcer. 2. The neutralization of acid and the inactivation of pepsin are brought about by the alkaline secretions. This process includes the slightly alkaline and diluting secretions of the stomach (mucous and mucoid secretion) and the regurgitation of bile, pancreatic juice and intestinal juice. 3. The products of peptic digestion per se inhibit peptic activity.

The Composition of Gastric Juice.—Normal gastric juice consists mainly of the following substances: hydrochloric acid, pepsin, mucin, inorganic salts, histamine, rennin, traces of lipase and an intrinsic factor which prevents pernicious anemia. The composition of the secretion from the different parts of the stomach varies according to the distribution of the various secretory cells in the stomach. Generally, the secretion of the cardia is alkaline and consists in great part of mucus; that of the fundus (this includes the fundus and the corpus according to anatomic terminology) is acid, and contains much pepsin and some mucus; the pyloric portion of the stomach secretes an alkaline mucus with no acid, but apparently the pylorus is important, though not essential, for the humoral phase of gastric secretion.¹

Of all the constituents of gastric juice, acid has been most widely studied. This is due to two factors: first, the ease with which determinations may be made by titration with standard alkali, and, second, the fact that the secretion of acid may be provoked by an easily controlled stimulus—the subcutaneous injection of histamine. Vanzant

and co-workers¹⁷ made an analysis of the normal range of acidity of the gastric contents after a test meal in almost 4,000 cases. The study of pepsin, however, is more difficult. There is no general agreement on the method of determining pepsin or the method of stimulating gastric juice with high peptic activity. Peptic activity depends principally on vagal activity, therefore drugs having effect on the parasympathetic system may be used; however, most of these drugs are inconvenient for general use because of their side reactions. Although the use of insulin appears to be the method of choice for stimulating the secretion of pepsin, it has not been used widely enough, and the hypoglycemic response of different subjects may be too variable to give standards of pepsin secretion such as are had for gastric acidity. The control and regulation of the various constituents of gastric juice have been described in detail by Babkin.⁵

II. ABNORMAL FACTORS WHICH INFLUENCE GASTRIC SECRETION

Organic Factors.—Acute gastric and duodenal ulcers have been produced by the administration of certain extracts of the posterior lobe of the pituitary gland¹⁸ and by pitressin.¹⁹ However, a reduction in the response to histamine has been observed after the injection of large amounts of posterior pituitary extract.²⁰ The experimental production of ulcer has been delayed or prevented by the administration of normal female or pregnancy urine extracts.²¹ A decrease of 85 per cent in the acidity of gastric juice during pregnancy with return to normal values shortly after term has been observed.²² This may have some relation to the infrequency of ulcer during pregnancy. Section of the pituitary stalk decreased the volume of gastric secretion,²³ but this may have been caused by the dehydration resulting from diabetes insipidus thus produced.

Ulceration of the gastrointestinal tract has been observed following adrenalectomy²⁴ and as a complicating factor in Addison's disease.²⁵

17. Vanzant, F. R.; Alvarez, W. C.; Eusterman, G. B.; Dunn, H. L., and Berkson, J.: Normal Range of Gastric Acidity from Youth to Old Age: Analysis of 3,746 Records, *Arch. Int. Med.* **49**:345 (March) 1932.

18. Franchini, G.: *Berl. klin. Wchnschr.* **47**:613, 670 and 719, 1910.

19. Nedzel, A. J.: Experimental Gastric Ulcer (Pitressin Episodes), *Arch. Path.* **26**:988 (Nov.) 1938.

20. Hess, W. R., and Gundlack, R.: *Arch. f. d. ges. Physiol.* **185**:137, 1920.

21. Broad, G. G., and Berman, L. G.: *Am. J. Digest. Dis.* **8**:27, 1941. Sandweiss, Saltzstein and Farbman.¹³

22. Krahmer-Petersen, cited by Faber, K., in Kraus, F., and Brugsch, T.: *Spezielle Pathologie und Therapie, innere Krankheiten*, Berlin, Urban & Schwarzenberg, 1914, vol. 5, p. 1015; cited by Ihre.²

23. Gross, E. G.; Ingram, W. R., and Fugo, N. W.: *Am. J. Physiol.* **133**:P118, 1941.

24. Mann, F. C.: *J. Exper. Med.* **23**:203, 1916.

25. Ask-Upmark, E.: *Acta chir. Scandinav.* **84**:55, 1940.

Hyperparathyroidism and hypercalcemia inhibited gastric secretion,²⁶ while hypocalcemia increased gastric secretion and diminished the concentration and total output of pepsin.^{26c}

There are some indications in the literature that hepatic function is sometimes involved in the production of ulcer.²⁷ Gerez and Weiss²⁸ studied the relation of gastric secretion to hepatic function by observing the effects of an Eck fistula on the secretory response of a Pavlov pouch. There was an increase in the volume, the acidity and the duration of the secretion. It may be that this hypersecretion was produced because the liver did not remove the gastric secretagogues from the blood so quickly or efficiently as in the normal animal.

Nutritional Factors.—Since Pavlov's original investigations there has been no doubt that the volume and the composition of gastric secretion are related to the type of food ingested. Jarotsky²⁹ based his dietary treatment of peptic ulcer on the principles of the Pavlovian school. The present knowledge of nutrition has taught that there are factors other than secretagogues which are present in food and which may influence gastric secretion. Among these other factors are the vitamins. Unfortunately, most studies of the effect of vitamins on gastric secretion have dealt with avitaminosis almost to the exclusion of hypervitaminosis. In view of the modern tendency to "shotgun" vitamin therapy, especially in the hands of the layman, and the use of highly purified and concentrated vitamin preparations, it would seem desirable to increase the knowledge of the effects of hypervitaminosis on gastric secretion. It has been shown that the administration of irradiated ergosterol decreases gastric acidity in man and that the decrease is proportional to the amount of ergosterol used.³⁰ Deficiency of thiamine causes anorexia with concomitant decrease in the gastric secretion, and there are some indications that a deficiency of thiamine or the vitamin B complex may result in inflammation and ulceration of the gastrointestinal tract.³¹ Deficiency of vitamin A has also been associated with a decrease in gastric acidity.³¹ The significance of the food factor as related to the general nutritional state of the body was indicated by

26. (a) Babkin, B. P.: *Rev. Gastroenterol.* **7**:373, 1940. (b) Babkin, B. P.; Komarov, O., and Komarov, S. A.: *Endocrinology* **26**:703, 1940. (c) Schiffrin, M. J.: *Am. J. Physiol.* **135**:660, 1942.

27. Boles, R. S.; Riggs, H. E., and Griffiths, J. O.: *Am. J. Digest. Dis.* **6**:632, 1939. Bollman, J. L., and Mann, F. C.: *Chronic Duodenal Ulcer in Animals with Eck Fistulas on Certain Diets*, *Arch. Path.* **4**:492 (Oct.) 1927. Ask-Upmark.²⁵

28. Gerez, L., and Weiss, A.: *Ztschr. f. d. ges. exper. Med.* **100**:281, 1937.

29. Jarotsky, A.: *Acta med. Scandinav.*, 1930, supp. 35, p. 1.

30. Bauer, W.; Marble, A.; Maddock, S. J., and Wood, J. C.: *Am. J. M. Sc.* **181**:399, 1931.

31. Wilbur, D. L.: *Am. J. Digest. Dis.* **6**:610, 1939.

Mann,³² McCarrison,³³ Fauley and Ivy³⁴ and Spira.³⁵ The different types of gastrointestinal lesions which seem related to some geographic factor³⁶ may in reality be due to the food habits prevalent in the locality, though this is entirely conjectural. Thus, Spira expressed the opinion that the familial incidence of ulcer (Hurst) also is caused by similar food habits. Secretagogues and vitamins, the type of food, how it is prepared and the mental state obtaining relative to its ingestion are not the only pertinent food factors. Every one who has worked with experimental gastric fistulas is well acquainted with the importance of maintaining an adequate mineral, salt and water intake. Deprivation of any of these factors will decrease gastric secretion. The importance of calcium was discussed by Gardner,³⁷ who made a study of functional disturbances of the gastrointestinal tract caused by a deficiency of calcium. Decker³⁸ produced acute ulcer in dogs by feeding hot (50 C.) gruel; however, the primary effect was congestion of the mucous membrane. The importance of fat in the normal mechanism of the humoral inhibition of gastric secretion has been indicated; therefore, it is of interest to note that a theory of the genesis of ulcer has been proposed³⁵ in which fat is supposedly the food factor responsible for the derangement of gastric function which produces ulceration!

Drugs.—Alcohol: Gastric secretion may be provoked by oral,³⁹ intrainestinal,⁴⁰ rectal⁴¹ and intravenous⁴² administration of alcohol. Dilute solutions (less than 15 per cent) stimulate a gastric secretion of high acidity and low peptic power.⁴³ It appears from indirect evidence

32. Mann, F. C.: *Minnesota Med.* **20**:755, 1937.

33. McCarrison, R.: *Studies in Deficiency Diseases*, London, Oxford University Press, 1921.

34. Fauley, G. B., and Ivy, A. C.: *Experimental Gastric Ulcer: Effect of Consistency of Diet on Healing*, *Arch. Int. Med.* **46**:524 (Sept.) 1930.

35. Spira, J. J.: *The Causation of Chronic Gastro-Duodenal Ulcers*, New York, Oxford University Press, 1931.

36. Walters, W.: *Surg., Gynec. & Obst.* **55**:355, 1932. Walters, W., and Sebening, W.: *Minnesota Med.* **15**:579, 1932.

37. Gardner, E. L.: *Minnesota Med.* **16**:698, 1933.

38. Decker, J.: *Berl. klin. Wchnschr.* **24**:369, 1887.

39. Cheney, W. F.: *The Diagnosis and Treatment of Diseases of the Stomach and Intestines*, in Christian, H. A.: *Oxford Monographs on Diagnosis and Treatment*, New York, Oxford University Press, 1928, vol. 2.

40. Ivy, A. C., and McIlvain, G. B.: *Am. J. Physiol.* **67**:124, 1923. Cheney.³⁹

41. Frouin, A., and Molinier, M.: *Compt. rend. Acad. d. sc.* **132**:1001, 1901. Radzikowski, C.: *Arch. f. d. ges. Physiol.* **84**:513, 1901.

42. Newman, H. W., and Mehrtens, H. G.: *Proc. Soc. Exper. Biol. & Med.* **30**:145, 1932. Petrovitch, A., and Bokanowa, E.: *Compt. rend. Soc. de biol.* **102**:633, 1929.

43. Babkin, B. P.: *Die äussere Sekretion der Verdauungsdrüsen*, ed. 2, in Gildemeister, M.; Goldschmidt, R.; Neuberg, C.; Parnas, J., and Ruhland, W.: *Monographien aus der Gesamtgebiet der Physiologie der Pflanzen und der Tiere*, Berlin, Julius Springer, 1928, vol. 15. Lönnquist, G.: *Skandinav. Arch. f. Physiol.* **18**:241, 1906.

that alcohol stimulates by causing the release of histamine from the tissues with which it comes in contact. High concentrations of alcohol irritate the gastric mucosa and provoke the secretion of mucus.⁴⁴ The prolonged administration of high concentrations may produce atrophic gastritis.⁴⁵ Obviously, alcohol is interdicted in the presence of ulcer by all physicians who believe that acid and irritants, such as alcohol, contribute to the chronicity of ulcer. It has been observed that the normal response of the secretion of mucus after the injection of pilocarpine nitrate is not seen in otherwise normal persons who habitually drink alcohol.⁴⁶ This indicates the presence of exhaustion of the mucous cells. The influence of alcohol on the digestive tract has been reviewed recently.⁴⁷

Tobacco: Hurst and Stewart⁴⁸ expressed the opinion that the excessive use of tobacco is of greater importance in causing duodenal ulcer than in causing gastric ulcer. A large majority of their patients with duodenal ulcer smoked to excess; of course, many people without duodenal ulcer smoke to excess. Many clinical reports regarding the management of patients with ulcer recommend the interdiction of smoking. However, the literature on the effect of smoking on the acidity of the gastric contents after a test meal is at variance, though the majority of reports indicate an increase in acidity.⁴⁹ It should be emphasized that an increase in the acidity of the gastric contents does not necessarily mean that gastric secretion has been stimulated. It may mean that smoking caused some pylorospasm or decreased the motility of the stomach, each of which would cause some retention of the acid secreted. It may also mean a decrease in the secretion of mucus and the diluting secretion. If smoking actually and directly stimulates gastric secretion in a decisive way, as does a meal or a small dose of histamine, it is odd that smoking does not stimulate the secretion of the fasting stomach.⁵⁰ The observation that smoking does not definitely stimulate gastric secretion is not sufficient reason to countermand the interdiction against smoking for the patient with ulcer.

Some Other Drugs: Morphine increases gastric secretion after a transient period of inhibition.⁵¹ The effect of morphine on the digestive

44. Barlow, O. W.: *J. Pharm.* **56**:117, 1936.

45. Thomsen, E.: *Acta med. Scandinav.* **61**:522, 1925.

46. Necheles, H., and Coyne, A.: Secretion of Mucus and Acid by Stomach in Healthy Persons and in Persons with Peptic Ulcer, *Arch. Int. Med.* **55**:395 (March) 1935.

47. Beazell, J. M., and Ivy, A. C.: *Quart. J. Stud. on Alcohol* **1**:45, 1940.

48. Hurst, A. F., and Stewart, M. J.: *Gastric and Duodenal Ulcer*, New York, Oxford University Press, 1929.

49. Ehrenfeld, A. B., and Sturtevant, M.: *Am. J. M. Sc.* **201**:81, 1941.

50. Schnedorf, J. G., and Ivy, A. C.: Effect of Tobacco Smoking on Alimentary Tract: Experimental Study of Man and Animals, *J. A. M. A.* **112**:898 (March 11) 1939.

51. Riegel, F.: *Ztschr. f. klin. Med.* **40**:347, 1900.

tract has been reviewed by Krueger.⁵² Sulfanilamide depresses gastric secretion.⁵³ The histamine antagonist thymoxyethyl-diethylamine does not affect the gastric response to histamine.⁵⁴

Psychic Factors.—The importance of the emotions in their relation to gastric function is a matter of common observation. Descriptions of the patient with ulcer usually include such characteristics as "high strung, nervous, worrying, aggressive, go-getter." This subject has been reviewed elsewhere.⁵⁵ Alexander⁵⁶ presented a speculative discussion of this subject from a psychiatric viewpoint. In the dog and in most human subjects, an emotional insult causes depression of the gastric secretion and motility. The report of Wittkower⁵⁷ is of special significance. His observations of human subjects indicated that emotions, such as fear, disgust and joy, did not always produce the same effect on gastric secretion. However, each person manifested a characteristic response, that is, an increase or a decrease of gastric secretion. This suggested that some inherent nervous or psychiatric factor predisposes to hypersecretion in the presence of emotional stimuli. This recalls Todd's observations regarding the effect of anxiety and stress on the motor activity of the stomachs of medical students. In the majority of students emotional states continued, after repeated exposure, to cause inhibition of the stomach. In a few subjects, however, who responded to stress by the manifestation of outward poise but with internal tension, the stomach became tonic and hypermotile. It was in the latter group that duodenal ulcer appeared when it appeared during the medical course. Ask-Upmark⁵⁸ observed a high incidence of ulcer among those "doing service behind the enemy lines" in the Russian-Finnish war. It is not unlikely that the heightened nervous tension of modern warfare will make peptic ulcer a major problem among the armed forces. Hurst⁵⁹ presented his experiences to date in the present war.

Effect of Surgical Procedures.—Vagotomy will abolish the cephalic phase of gastric secretion and consequently reduce the total volume of secretion in the response to a meal. For this reason, its value (in conjunction with other operative procedures) has been considered.⁵⁹

52. Krueger, H.: *Physiol. Rev.* **17**:618, 1937.

53. Davenport, H. W.: *Am. J. Physiol.* **133**:P69, 1941.

54. Chickering, O., and Loew, E. R.: *Am. J. Physiol.* **133**:P51, 1941.

55. (a) Alvarez, W. C.: *Nervous Indigestion*, New York, Paul B. Hoeber, Inc., 1930; *Am. J. Surg.* **18**:207, 1932. (b) Carlson, A. J.: *The Control of Hunger in Health and Disease*, Chicago, University of Chicago Press, 1916; *Physiol. Rev.* **3**:1, 1923. (c) Eusterman, G. B., and Balfour, D. C.: *The Stomach and Duodenum*, Philadelphia, W. B. Saunders Company, 1935.

56. Alexander, F., in Portis, S. A.: *Diseases of the Digestive System*, Philadelphia, Lea & Febiger, 1941.

57. Wittkower, E.: *J. Ment. Sc.* **81**:533, 1935.

58. Hurst, A. F.: *Am. J. Digest. Dis.* **8**:321, 1941.

Obviously, the success of vagotomy in the treatment of ulcer will depend on the relative importance of the cephalic phase or vagal activity before operation and on the factors occurring as a result of vagotomy which may influence gastric secretion. It has been demonstrated that the vagi are necessary for the maintenance of normal gastric tone and that the rate of the evacuation of some foods from the stomach is retarded by vagotomy.⁶⁰ The prolonged presence of food in the stomach, unless this is prevented by an additional operation, will increase the gastric phase of secretion and thus tend to defeat the original purpose of vagotomy. Since vagal stimulation produces vasodilation of the blood vessels of the stomach,⁶¹ vagotomy might decrease, at least temporarily, the blood supply to the gastric and the intestinal mucosa owing to the unopposed constrictor activity of the splanchnic nerves.

The gastric phase of secretion can be reduced by gastroenterostomy, provided this procedure decreases the gastric emptying time and the intragastric tension. The operation favors also the regurgitation of the alkaline duodenal contents. On theoretic grounds this operative procedure is most likely to be of value in the presence of high grade pyloric achalasia or stenosis and a stomach that does not secrete acid excessively. In dogs, gastroenterostomy cannot be relied on to decrease gastric secretion either in the presence or the absence of partial pyloric stenosis.⁶² Matthews and Dragstedt⁶³ demonstrated experimentally the importance of the regurgitation of the alkaline duodenal contents. When a valve which prevented regurgitation was placed in the pylorus, the healing time of experimentally produced gastric ulcers was often delayed to twice that required when normal regurgitation took place. McCann⁶⁴ made an extensive study of the effects of various types of enterostomy on experimental animals. Gastroenterostomy seems to be contraindicated in the presence of true hypersecretion, since it does not attack the cause of the secretion and exposes the vulnerable jejunum to the proteolytic action of the gastric juice.

Subtotal gastrectomy is performed so that regurgitation may occur more readily, the emptying time of the stomach may be reduced, the

59. Best, R. R., and Orator, V.: *Ann. Surg.* **96**:184, 1932. Klein, E.: *Gastric Secretion After Partial Gastrectomy*, *J. A. M. A.* **89**:1235 (Oct. 8) 1927; *Ann. Surg.* **90**:65, 1929. Shapiro, P. F., and Berg, B. N.: *Return of Gastric Acidity After Subtotal Gastrectomy and Double Vagotomy*, *Arch. Surg.* **28**:160 (Jan.) 1934. Winklestein, A., and Berg, A. A.: *Am. J. Digest. Dis.* **5**:497, 1938.

60. Meek, W. J., and Herrin, R. C.: *Am. J. Physiol.* **109**:221, 1934.

61. Stahnke, E.: *Arch. f. klin. Chir.* **132**:1, 1924. Vineberg, A. M.: Ph.D. Thesis, McGill University Graduate School, Montreal, 1933, p. 53.

62. Medoff, J.; Neuwelt, F.; Ptedjl, J., and Necheles, H.: *Am. J. Physiol.* **133**:386, 1941.

63. Matthews, W. B., and Dragstedt, L. R.: *Surg., Gynec. & Obst.* **55**:265, 1932.

64. McCann, J. C.: *Experimental Peptic Ulcer*, *Arch. Surg.* **19**:600 (Oct.) 1929.

ulcer-bearing area may be excised, part of the humoral mechanism of gastric secretion may be removed and some of the acid-secreting area may be excised. Recently, Lewis⁶⁵ excised the mucosa of the pyloric antrum and observed a decrease in the volume of secretion. This indicates the importance of the pyloric mucosa. More recently,¹ evidence has been obtained which indicates that the pyloric mucosa contributes to, but is not the sole origin of, the humoral mechanism of gastric secretion. Connell⁶⁶ made use of a subtotal gastrectomy, fundusectomy, which removes most of the acid-secreting area of the stomach. Wangenstein⁶⁷ also employed this procedure and found, as might be expected, a high incidence of anacidity, at least for a number of months after the operation.

It is certain that partial gastrectomy will reduce the gastric phase of secretion. The extent to which this takes place will depend chiefly on the extent to which the acid-secreting area has been resected and on the eventual degree of hypertrophy and hyperplasia of the gastric remnant. The degree of hypertrophy may depend on the rate of emptying of the remnant and the size and the character of the meal.¹ Attempts to correlate the acidity of the gastric contents with the clinical results following subtotal gastrectomy were not uniformly attended with success according to a more recent report.⁶⁸ This is not surprising in view of the manifold factors which are operating before and after partial gastrectomy in the patient with ulcer.

Other Factors.—Roentgen rays⁶⁹ and fever⁷⁰ depress gastric secretion. A decrease in the red blood cell count⁷¹ and anoxemia⁷² reduce gastric acidity. Cholecystitis and cholelithiasis do not uniformly or characteristically affect gastric acidity.⁷³ Burns produce hypersecretion.⁷⁴ There is no apparent relation between gastric acidity and height

65. Lewis, E. B.: *Surgery* **4**:692, 1938.

66. Connell, F. G.: *Surg., Gynec. & Obst.* **49**:696, 1929; *Ann. Surg.* **96**:200, 1932.

67. Wangenstein, O. H.: *Surg., Gynec. & Obst.* **70**:59, 1940.

68. Strauss, A. A.; Strauss, S.; Levitsky, P.; Sheman, L.; Seidman, E. E.; Arens, R. A., and Meyer, J.: *Am. J. Digest. Dis.* **4**:32, 1937.

69. Portis, S. A., and Arens, R.: *Am. J. Roentgenol.* **11**:272, 1924. Palmer, W. L., and Templeton, F.: Effect of Radiation Therapy on Gastric Secretion, *J. A. M. A.* **112**:1429 (April 15) 1939. Snell, A. M., and Bollman, J. L.: *Am. J. Digest. Dis.* **1**:164, 1934.

70. Meyer, J.; Cohen, S. J., and Carlson, A. J.: Gastric Secretion in Fever, *Arch. Int. Med.* **21**:354 (March) 1918.

71. Apperly, F. L., and Cary, M. K.: *Am. J. Digest. Dis.* **3**:466, 1936.

72. Pickett, A. C., and Van Liere, E. J.: *Am. J. Physiol.* **123**:163, 1938.

73. Sagal, Z.; Marks, J. A., and Kantor, J. L.: *Ann. Int. Med.* **7**:76, 1933. Vanzant, F. R.; Alvarez, W. C.; Berkson, J., and Eusterman, G. B.: Changes in Gastric Acidity in Peptic Ulcer, Cholecystitis and Other Diseases Analyzed with Help of New and Accurate Technique, *Arch. Int. Med.* **52**:616 (Oct.) 1933.

74. Necheles, H., and Olson, W. H.: *Am. J. Physiol.* **133**:396, 1941.

and weight in man.⁷⁵ Brunschwig and associates⁷⁶ reported that the intravenous injection of an extract of the gastric juice of patients with either pernicious anemia or gastric carcinoma inhibits the gastric secretion in dogs.

III. GASTRIC SECRETION IN THE PRESENCE OF ULCER AND ITS RELATION TO THE CAUSATION OF ULCER

Gastric Secretion in the Presence of Ulcer.—Sagal, Marks and Kantor⁷³ studied the clinical significance of the acidity of the gastric contents in patients with digestive symptoms. A modified Boas-Ewald test meal was used, and a table of standard values of the secretory response was prepared. Acid values higher than those usually found in normal subjects were common in the presence of ulcer, particularly duodenal ulcer. Hypersecretion of the interdigestive phase has been observed with duodenal ulcer.⁷⁷ This is in agreement with the earlier work of Dragstedt and Vaughn,⁷⁸ who demonstrated an increase in the secretion of a Pavlov pouch in the presence of experimental ulcer. Necheles and Maskin⁷⁹ reported an increase in the cephalic phase of secretion in patients with ulcer. However, they stated their belief that this is not a major factor in the genesis of ulcer. This view is not in agreement with that of Babkin⁵ and Winkelstein,⁸⁰ who expressed the opinion that the vagus may play an important role in the genesis of ulcer. This is supported by Cushing's⁸¹ observations of various types of ulcer in the presence of lesions of the midbrain, although the occurrence of ulcer under such conditions is not a uniform experimental finding.

Thre² made an extensive study of the effects of ulceration on gastric secretion in man. Analysis was made of the fasting secretion and that provoked by histamine and insulin. Some of his data have been recalculated and are presented in the table.

The volume of secretion was not materially affected by gastric ulceration; however, in the presence of duodenal ulcer, the three types of secretion were greater than normal. Gastritis, uncomplicated by

75. Vanzant, F. R.; Alvarez, W. C., and Berkson, J.: *Am. J. Digest. Dis.* **3**:83, 1936.

76. Brunschwig, A.; Clarke, T. H.; Van Prohaska, J., and Schmitz, R. L.: *Surg., Gynec. & Obst.* **70**:25, 1940. Brunschwig, A.; Van Prohaska, J.; Clarke, T. H., and Kandel, E.: *J. Clin. Investigation* **18**:415, 1939.

77. Bloomfield, A. L.; Chen, C. K., and French, L. R.: *J. Clin. Investigation* **19**:863, 1940.

78. Dragstedt, L. R., and Vaughn, A. M.: *Gastric Ulcer Studies*, *Arch. Surg.* **8**:791 (May) 1924.

79. Necheles, H., and Maskin, M. H.: *Am. J. Digest. Dis.* **3**:90, 1936.

80. Winkelstein, A.: *Am. J. M. Sc.* **185**:695, 1933; *New York State J. Med.* **37**:1989, 1937.

81. Cushing, H.: *Surg., Gynec. & Obst.* **55**:1, 1932.

ulcer, showed hyposecretory responses. The hypersecretion associated with duodenal ulcer and the normal secretion associated with gastric ulcer have been observed by others. However, there is no satisfactory explanation of this phenomenon. The failure of atropine to abolish the interdigestive secretion in duodenal ulcer has been taken as evidence that histamine or some histamine-like substance may be responsible for the secretion.¹ A histamine cycle has been suggested in which the irritated mucosa liberates histamine which in turn stimulates gastric secretion; the action of the gastric juice on the ulcer liberates more histamine, and thus the cycle continues. This might explain the hypersecretion of the fasting state in duodenal ulcer, but why does not gastric ulcer produce the same effect? Is it not possible that gastric ulcer, too, might liberate histamine? The presence of gastritis involving the acid-secreting mucosa might be involved; this would reduce the secretory response to excitants.

Ulceration may act also in other ways to influence the gastric secretion and the acidity of the gastric contents. The emptying time of the

Effects of Ulcer on the Gastric Secretion of Human Beings

Condition	Average Volume of Response; Percentage of Normal		
	Fasting	Histamine	Insulin
Gastric ulcer	100	100	120
Duodenal ulcer	170	155	141
Gastritis (without ulcer).....	69	58	54

stomach is delayed in some patients in the presence of ulcer,⁸² and this tends to increase the gastric phase of secretion. The production of mucus is also impaired, at least in relation to the production of acid, in patients with ulcer,⁴⁶ and this might increase the acidity of the gastric juice. There are some indications in the literature of a tendency of the acidity of the gastric contents to diminish as the ulcer enters a remission under management. Brown and Dolkart⁸³ reported that gastric acidity tends to moderate as the gastrointestinal tract returns to normal, but they were not able to observe any significant trend in the gastric acidity prior to a recurrence of ulcer activity.

Relation of Gastric Secretion to the Causation of Ulcer.—There are many mechanisms which may be concerned in the production of the primary defect in the stomach or the duodenum, but why this defect sometimes develops into an ulcer and other times heals spontaneously is uncertain. One thing is certain—the actual destruction of the tissue results from the proteolytic (hydrochloric acid and pepsin) action of the

82. Ivy, A. C.: *Physiology of the Stomach: Studies on Gastric Ulcer*, Arch. Int. Med. 25:6 (Jan.) 1920.

83. Brown, C. F. G., and Dolkart, R. E.: *Gastric Acid During Recurrences and Remissions of Duodenal Ulcer*, Arch. Int. Med. 60:680 (Oct.) 1937.

gastric juice. A large amount of experimental evidence has shown that the corrosive action of gastric juice is of prime importance in the genesis of postoperative jejunal ulcer and that gastric juice is undoubtedly a chronicity factor in delaying the healing of experimental gastric lesions.

Much emphasis has been placed on the acidity of the gastric juice without regard to peptic activity. Mann^{83a} expressed the opinion that the importance of acid in the causation of ulcer cannot be overemphasized. The fact that ulcer has been produced by a technic which allows for the continuous absorption of histamine⁸⁴ has been used to strengthen the supposition that acid is the cause of ulcer; however, histamine juice contains ample pepsin. The role of acid per se has been emphasized by Dragstedt.⁸⁵ The large accumulation of clinical evidence showing the beneficial effects of neutralization and buffering substances also has served to emphasize the importance of acid. Yet the proteolytic power of gastric juice is due not to acid alone, but to pepsin in acid solution. The difference in the irritating properties of acid and acid and pepsin has been demonstrated recently by experiments in which loops of jejunum were perfused with either acid or acid and pepsin.⁸⁶ Bleeding or ulceration were never produced by the concentration of acid used, while ulceration always followed the perfusion when pepsin was added to the acid. As a matter of fact, ulceration of the gastrointestinal tract has never been produced by physiologic concentrations of acid in the complete absence of pepsin. That pepsin may play a significant role is further indicated by the high incidence of hyperpepsinia in connection with duodenal ulcer.² It seems desirable to use some therapeutic agent that will neutralize acid and be able to inactivate pepsin. Some aluminum compounds have these properties.⁸⁷

In conclusion, it should be stated that this discussion of the physiology of gastric secretion and the relation of hydrochloric acid and pepsin to the problem of ulcer is not intended to imply that the excessive secretion of gastric juice or its retention in the stomach is the cause of gastroduodenal ulcer. It is our opinion, based on our own studies and the evidence in the literature, that the irritating action of acid and pepsin is the prime factor in the genesis of postoperative jejunal ulcer and is an important factor in the development, persistence and perforation of gastric or duodenal ulcer.

83a. Mann, F. C., in Eusterman and Balfour.^{55c}

84. Varco, R. L.; Code, C. F.; Walpole, S. H., and Wangenstein, O. H.: *Am. J. Physiol.* **133**:P287, 1941.

85. Dragstedt, L. R., and Matthews, W. B.: *Am. J. Physiol.* **105**:29, 1933.

86. Schiffrin, M. J.: *Proc. Soc. Exper. Biol. & Med.* **45**:592, 1940. Schiffrin, M. J., and Warren, A. A.: *Am. J. Physiol.* **133**:P437, 1941; *Am. J. Digest. Dis.*, to be published.

87. Komarov, S. A., and Komarov, O.: *Am. J. Digest. Dis.* **7**:166, 1940. Schiffrin, M. J., and Komarov, S. A.: *ibid.* **8**:215, 1941.

MOTOR PHYSIOLOGY OF THE STOMACH, THE PYLORUS AND THE DUODENUM

WITH SPECIAL REFERENCE TO GASTRODUODENAL ULCER

J. P. QUIGLEY, PH.D.

CLEVELAND

Numerous experimental methods are known which lead to ulceration of the stomach. Of these methods, the greatest significance is attached to those employed by Exalto, Mann, Ivy, Dragstedt and others, who produced chronic peptic ulcer by experimental alterations in gastrointestinal function. The ulcer thus produced resembles grossly and histologically the clinical lesion, and both respond in a similar manner to therapy. From such studies more is already known regarding the basic factors causing or curing the experimental lesion than those influencing the spontaneous ulcer, and the information available with respect to both lesions exceeds that regarding ulcer in other and frequently more accessible portions of the body.

The studies on experimentally produced ulcers have greatly revived interest in the fundamental ulcer problems—why ulcers form, become chronic, undergo hemorrhage or perforate and how they can be prevented or healed. So far, the investigations have been most fruitful in establishing the fundamental alterations in gastrointestinal function which are essential in the genesis of this condition. Since such knowledge may be considered a prerequisite to an ultimate solution of the problems involved, satisfactory forward strides appear imminent, and attainment of the goal does not appear impossible.

As yet, no specific cause or therapy of the chronic clinical condition has been established from experimental or clinical observations. The divergence in the teachings among outstanding clinicians regarding what constitutes the therapy of choice for ulcer and the avidity with which new therapeutic procedures are greeted constitute adequate comment on the present status. However, the physiologic method of approach to this problem has been gradually replacing empiricism and has placed the investigations on a more satisfactory scientific level. While the mode of attack was limited to empiric methods, much valuable information accrued, but such studies were so handicapped by an inability adequately to control or check many essential aspects and to distinguish objective results from subjective impressions that forward steps were

From the Department of Physiology, Western Reserve University School of Medicine.

necessarily slow and uncertain. The most significant progress can be anticipated when clinical observations and animal studies by competent investigators are carefully integrated and correlated so that each can act both as an inspiration and as a check on the other.

Among the methods of producing experimental ulcer, the procedures which simulate most closely the clinical conditions are those involving extensive mechanical and chemical trauma to the digestive tract. The major emphasis has been placed on gastric acidity, but ulcer does not develop in all cases of hyperacidity, and ulcer may heal in the presence of hyperacidity. Apparently acidity is only one of the factors involved. An important role is also played by the motor activities of the intestine, especially those involving spasm, hypermotility and atonia. Thus the physiologic factors developing the propulsive force, resulting from the force with which food is propelled, or those causing stagnation require special emphasis. It is the purpose of this report to relate to the ulcer problem the normal and abnormal manifestations of these motor activities.

Clinically, peptic ulcer develops chiefly in the distal part of the esophagus, the stomach and the proximal part of the duodenum. These organs have as a common function the transportation of food, and in the esophagus and the duodenum this propulsion is the paramount motor function. In addition to propulsion, the stomach has the important motor task to store food, to break it up into fragments and to mix it with gastric juice. Further, there are certain movements of the esophagus, the stomach and the duodenum designated as hunger contractions which have the important function of initiating hunger sensations and thus apprising the subject that realimentation is desirable.

HUNGER AND APPETITE

The intake of food is normally accurately related to the metabolic needs of the person. This is evidenced by the fact that the body weight of an adult remains relatively constant over extended intervals in spite of considerable variations in metabolic requirements. So well is this fact recognized that sudden changes in body weight are considered with suspicion by both the patient and the clinician. On the other hand, the growing child, the convalescent patient, the person performing heavy manual labor or the pregnant woman all require a relative increase in caloric intake, and in such persons the subjective demand for food likewise parallels the need.

The factors involved in the regulation of the intake of food and its correlation with metabolic needs are important and have been extensively investigated. The regulation is achieved through the sensations of appetite and hunger. In a broad sense, these are considered as the sum total of the conditions determining the ingestion of food. Since they

persist during the entire span of life of the subject and may exert a predominant control over his activities, they constitute the most potent influence in life. The entire behavior of man and animals is fundamentally related to the preservation of the life of the individual and the perpetuation of the species. This behavior may be resolved into the activities related to satisfying the demands for food, water, salt and sex gratification. Normally these activities are modified by training and culture, but this veneer is readily hidden under circumstances which release from confinement the powerful driving forces which constitute the fundamental urges. The behavior of the members of the Donner party in 1846-1847 when misfortune interrupted their migration to California may be considered as a demonstration of the force of primitive hunger. "The horror of these people eating each other's brains, entrails, legs and other tissues is scarcely less than the horror of the callous and grasping way in which some of them behaved in the face of starvation."

Hunger is an unpleasant sensation of emptiness, gnawing tension and discomfort or dull pain in the epigastric region. A feeling of lassitude, weakness, faintness, headache or nausea may also be present and may even dominate the picture. There is a general increase in irritability of the central nervous system and vasomotor instability. Cannon,¹ Carlson² and their students have been particularly active in demonstrating that the sensation of hunger results directly from peculiar movements (hunger contractions) occurring in the lower part of the esophagus, the stomach and the duodenum. These contractions initiate impulses which are carried over the vagi to the medulla where they affect respiratory and cardiovascular centers, then pass to the midbrain and the thalamus, where they are appreciated as rather generalized, crude or protopathic sensations. However, there is some localization to the epigastrium, and a trained person can distinguish between gastric and duodenal contractions.³ A similar localization of pain from faradic stimulation of the stomach or the duodenum of human subjects was noted by Boyden.⁴

Animals appear to experience hunger after extirpation of the stomach, denervation of the stomach and also after vagotomy, splanchnicotomy and celiac ganglionectomy. This and other related evidence

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2. Carlson, A. J.: *The Control of Hunger in Health and Disease*, Chicago, University of Chicago Press, 1916.

3. Quigley, J. P., and Solomon, E. I.: *Action of Insulin on the Motility of the Gastro-Intestinal Tract: V. (a) Action on the Human Duodenum; (b) Action on the Colon of Dogs*, *Am. J. Physiol.* **91**:488 (Jan.) 1930.

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suggests that a mechanism, probably centrally located, in addition to the hunger contractions produces the hunger sense and behavior in the normal person.⁵

Appetite is a cerebral phenomenon, a conditioned reflex developed largely on previous feeding experiences which caused the disappearance of the hunger distress and its replacement by a feeling of well-being. Appetite is also based on the agreeable smell, the taste and the appearance of food, on habit and many other factors and in general is a pleasant experience. In the normal civilized person having three meals daily, the ingestion of food is dependent chiefly on habit and appetite.

Hunger is especially important in the infant before appetite has developed. It produces restlessness, causes the infant to attempt to eat many substances and by experience to learn what and how to eat and finally to develop appetite. Richter's⁶ experiments were illustrative in this respect, for he found that the physical activity of rats was greatest during the hunger period but that after eating they fell asleep.

Hunger contractions develop in the empty stomach at a variable interval after gastric emptying. This latent period, the vigor of contractions and the relative duration of hunger and rest periods are usually directly related to the metabolic needs of the subject (age, length of fast, metabolic rate, etc.). Usually a thirty to forty-five minute period of activity alternates with a thirty to sixty minute rest period. The hunger contractions are peristaltic in nature and start weakly in the region of the cardia or the lower part of the esophagus, sweep with augmenting strength over the entire stomach and gradually die out in the duodenum. In the normal person, the ordinary contractions produce intermittent distress or gnawing sensations, while the incomplete tetany which frequently terminates the period is definitely painful.

A satisfactory explanation is still wanting for the fact that hunger contractions initiate disagreeable sensations while digestive contractions do not. Digestive contractions were compared with hunger contractions by Rogers and Hardt⁷ and Mulinos,⁸ but no significant difference was

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6. Richter, C. P.: Animal Behavior and Internal Drives, *Quart. Rev. Biol.* **2**:307, 1937.

7. Rogers, F. T., and Hardt, L. L. J.: Contributions to the Physiology of the Stomach: XXVI. The Relation Between the Digestion Contractions of the Filled, and the Hunger Contractions of the "Empty" Stomach, *Am. J. Physiol.* **38**:274 (Aug.) 1915.

8. Mulinos, M. G.: The Gastric Hunger Mechanism: The Effect of Food upon the Empty Stomach and Its Relation to Hunger, *Am. J. Physiol.* **83**:115 (Dec.) 1927.

noted. Brody, Werle, Meschan and Quigley⁹ studied the contractions by the fluoroscopic technic and simultaneously accurately determined the pressures in the pyloric antrum and the duodenal bulb by the optical registration method and found the motility similar during fasting and after feeding. However, in the latter state the basal pressures were increased, and the phasic pressure changes became more uniform.

Hunger contractions are inhibited most effectively by the ingestion of food and more transiently by the sight of food, by drinking water, by smoking, by psychic disturbances or by a variety of stimuli, especially those involving pain from any part of the body. The inhibition of hunger contractions by food does not result from food confined to the stomach. Distention of the stomach by any substance, such as a large balloon, fluid or gas, increases the frequency and magnitude of hunger contractions. However, the presence of food in the duodenum promptly and characteristically suppresses the motility. This inhibition is induced through the enterogastric reflex and through enterogastrone, which will be considered in greater detail in a later section of this paper.

The mechanism controlling the spontaneous initiation and termination of hunger contractions is unknown. Vagotomy tends to depress and splanchnicotomy to augment this motility in a characteristic manner. Nevertheless, hunger contractions occurring in the completely denervated stomach are strikingly similar in the transplanted gastric pouch and the main stomach from which it was made.¹⁰ This indicates the action of an unidentified humoral factor. Tschukitscheff¹¹ presented evidence that transfusion of blood produced or inhibited hunger contractions in the recipient animal, depending on whether the blood was taken while the donor was showing active hunger contractions or was in a period of gastric rest. The active factor apparently is not the blood sugar level¹² or the amino acid concentration of the blood.¹³

9. Brody, D. A.; Werle, J. M.; Meschan, I., and Quigley, J. P.: Interlumen Pressures of the Digestive Tract, Especially the Pyloric Portion, *Am. J. Physiol.* **130**:791 (Oct.) 1940.

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The evidence is convincing that hunger contractions through mechanical trauma to the area involved may give rise to considerable distress in the patient with ulcer and may also prevent healing of the ulcer. Hunger contractions should therefore be controlled. It is desirable but not practical to produce complete motor rest of the stomach in the patient with ulcer. The next best procedure, fortunately, is usually rather satisfactory and is extensively employed clinically. This consists of suppression of hunger contractions and a change of motility to the digestive type by frequent feedings.¹⁴ It is especially desirable to avoid or relieve the conditions which tend to exaggerate hunger contractions (fasting or augmentation of the metabolic rate by hard physical labor, hyperthyroidism, exposure to cold, insulin hypoglycemia or diabetes).

Increase in gastric peristalsis and shortening of evacuation time roughly in proportion to the degree of hunger were noted by Ivy and Fauley.¹⁵ Avoidance of this hypermotility with its attendant trauma to the sphincter region is one of the advantages of frequent feeding. Mann and Bollman observed that frequent feeding, especially of protein, may be beneficial in another way, for if dogs are fed, the capacity of the stomach to neutralize acid is exaggerated, even though the residues of food are flushed from the stomach.

Many patients with ulcer are well aware of the symptomatic relief which can be obtained by the ingestion of food and customarily take full advantage of this subterfuge. This results in the ingestion of food, not primarily to balance unsatisfied metabolic needs but strictly to relieve somatic discomfort. In a patient with such a condition, hunger contractions have again become dominant in determining the intake of food—a superficial approximation of the primitive or infantile state. Owing to inaccuracies in the precise appreciation of ulcer pains, the food may be ingested even on occasions when the pain is not of the type amenable to food.

According to Norpoth,¹⁶ Henning,¹⁷ Scholtz and Brugsch,¹⁸ Mensing and Kelly¹⁹ and Hillman,²⁰ jejunal feeding produces motor and secretory

14. Sippy, B. W.: Gastric and Duodenal Ulcer: Medical Cure by an Efficient Removal of Gastric Juice, *J. A. M. A.* **64**:1625 (May 15) 1915. Meulengracht, E.: Treatment of Hematemesis and Melaena with Food, *Acta med. Scandinav.*, 1934, supp. 59, p. 375. Treatment of Hematemesis and Melaena with Food: Mortality, *Lancet* **2**:1220 (Nov. 30) 1935.

15. Ivy, A. C., and Fauley, G. B.: The Effect of Hunger on the Emptying Time of the Stomach, *Am. J. Physiol.* **91**:206 (Dec.) 1929.

16. Norpoth, L.: Ueber jejunale Steuerung des Magenmotilität, *Deutsches Arch. f. klin. Med.* **176**:52, 1933.

17. Henning, N., and Norpoth, L.: Untersuchungen über die sekretorische Function des Magens während des nächtlichen Schlafes, *Arch. f. Verdauungskr.* **42**:12, 1928.

18. Scholtz, H. G., and Brugsch, J.: Untersuchungen bei der Jejunalsondenbehandlung des Ulcus ventriculi, *Deutsches Arch. f. klin. Med.* **175**:202, 1933.

(Footnotes continued on next page)

rest of the stomach, relieves the ulcer distress and promotes healing. However, these claims were not substantiated by Zuckschwerdt and Eck.²¹ At least a portion of the gastric inhibition produced by jejunal feeding results from intestinal distention. Schnedorf and Ivy²² observed a decrease in hunger contractions or a delay in gastric evacuation from excessive smoking, but they were unable to explain why smoking usually exacerbates the ulcer condition.

ULCER PAIN

The pain fibers of the gastrointestinal tract ordinarily are insensitive to chemical or moderate mechanical stimuli. Hurst²³ considered that tension of the wall of the intestine constitutes the only adequate stimulus, and this concept is widely accepted but by no means proved. Good evidence has shown that either mechanical or chemical factors can induce ulcer distress, and it is possible that they produce their effect by augmenting the tension of the wall of the intestine. The pain experienced during fasting might result from hunger contractions or from acid in contact with the ulcer, and the ingestion of food may afford relief either by terminating the contractions or by adsorbing, neutralizing and diluting the gastric acid. The gnawing, intermittent type of ulcer pain is generally ascribed to hunger contractions; the continuous burning sensation may arise either from a spasm in the region of the ulcer, from the swelling and inflammation around the border of the ulcer or from contact of the ulcer with gastric acid. Since the hydrochloric acid-pepsin mixture exerts an anesthetic action on the human skin and does not produce pain in the normal stomach, it is suggested that in the patient with ulcer, gastric acid must act indirectly and produce pain by inducing abnormal motility in the vicinity of the ulcer.

Ulcer pain has been definitely correlated with hunger contractions.²⁴ Most investigators have found the hunger contractions of patients with

19. Mensing, E. H., and Kelly, E. H.: Total Suppression of Acid Gastric Secretion and Hunger Contractions by Means of Jejunostomy: Experimental and Clinical Study, *Am. J. Surg.* **20**:99 (April) 1933.

20. Hillman, O. S.: Jejunostomy in Treatment of Massive Gastric Ulcer, *Brit. M. J.* **1**:221 (Feb. 11) 1933.

21. Zuckschwerdt, L., and Eck, T.: Die operative Behandlung des nicht-resezierbaren peptischen Geschwüres, *Deutsche Ztschr. f. Chir.* **237**:457, 1932.

22. Schnedorf, J. G., and Ivy, A. C.: Effect of Tobacco Smoking on Alimentary Tract: Experimental Study of Man and Animals, *J. A. M. A.* **112**:898 (March 11) 1939.

23. Hurst, A. F.: *The Sensibility of the Alimentary Canal*, London, Oxford University Press, 1911.

24. Carlson, A. J.: Contributions to the Physiology of the Stomach: XLIV. The Origin of the Epigastric Pains in Cases of Gastric and Duodenal Ulcer, *Am. J. Physiol.* **45**:80 (Dec.) 1917. Ginsburg, H.; Tumpowski, I., and Hamburg, W. W.:

ulcer normal or only slightly exaggerated, but Onodera²⁵ described an augmented type of motility which he considered typical of this disorder. The development of ulcer pains from normal hunger contractions is ascribed to concomitant hyperexcitability of the sensory mechanism in the gastrointestinal wall. This hypersensitivity may result from gastritis, the swelling and inflammation surrounding the ulcer, the action of hydrochloric acid²⁶ or similar factors.

In general, these conclusions are in accord with the significant observations of Dragstedt and Palmer²⁷ of a patient with an ulcer exposed under local anesthesia. Gentle rubbing of the ulcer with the finger produced severe and typical distress and severe pain resulted from compression or massage of the ulcer or traction on the duodenum. The introduction of sodium bicarbonate into the stomach relieved the distress, even though the traction was continued. The application of hydrochloric acid to the ulcer returned the distress, and this was again relieved by bicarbonate of soda. Later, a deep circular contraction ring developed just distal to the ulcer and was succeeded by several similar spasms, and all during this interval severe, cramplike pain persisted.

Clinicians frequently report the development of pyloric achalasia, spasm or stenosis from ulcer in close proximity to the sphincter. If such a condition exists, the hunger contractions are probably exaggerated and gastric evacuation retarded,²⁸ and a mechanism is available for augmentation of the ulcer distress.²⁹

Contributions to the Physiology of the Stomach: XXV. The Newer Interpretation of the Gastric Pain in Chronic Ulcer, *J. A. M. A.* **67**:999 (Sept. 30) 1916. Dundon, J. R.: Contributions to the Physiology of the Stomach: XLIII. The Influence of Experimental Ulcers of the Stomach and Duodenum on the Hunger Contractions of the Empty Stomach, *Am. J. Physiol.* **44**:234 (Sept.) 1917. Christensen, O.: Pathophysiology of Hunger Pains, *Acta med. Scandinav.*, 1931, supp. 37, p. 1. Dimitriu, C. C.; Tanasoca, T., and Popovici, A.: La douleur gastrique, étudiée par la méthode viscérographique, *Presse méd.* **46**:610 (April 20) 1938.

25. Onodera, N.; Kanegae, S.; Matufuzi, M., and Hasi, T.: Ueber die gastrographische Methode der Diagnose von Magenkrebs, Magen-Darm-Geschwür und Cholecystitis, *Ztschr. f. klin. Med.* **118**:354, 1931.

26. Palmer, W. L.: The Mechanism of Pain in Gastric and Duodenal Ulcer: I. Achlorhydria; II. The Production of Pain by Means of Chemical Irritants; III. The Role of Peristalsis and Spasm, *Arch. Int. Med.* **39**:109 (Jan.) 1927.

27. Dragstedt, L. R., and Palmer, W. L.: Direct Observations on the Mechanism of Pain in Duodenal Ulcer, *Proc. Soc. Exper. Biol. & Med.* **29**:753 (March) 1932.

28. (a) Elsesser, O. J.: Contributions to the Physiology of the Stomach: XXXI. The Effect of Experimental Partial Stenosis of the Pylorus on the Motility of the Empty Stomach, *Am. J. Physiol.* **39**:303 (Jan.) 1916. (b) Carlson, A. J., and Ginsburg, H.: Contributions to the Physiology of the Stomach: XXX. The Tonus and Contractions of the Empty Stomach of Infants with Congenital Pyloric

THE STOMACH DURING DIGESTION AND EVACUATION

The motor activities of the stomach during digestion, consisting of the reception of a meal, the maceration, the fragmentation and the mixing of the food with the gastric juice and the discharge of the chyme into the duodenum may be detailed as follows: As food passes from the esophagus into the empty stomach, the walls which were in apposition are separated, and the stomach fills with a moderate increase in basal intragastric pressure.³⁰ The property of the stomach which enables it to function as a reservoir (to fill without a significant increase in pressure) has been ascribed, especially by Cannon, to "receptive relaxation," a loss of tone of the gastric wall initiated by a reflex from the esophagus. An inhibitory reflex is definitely involved, for a fall of intragastric pressure follows the smelling of food, and the intragastric pressures are transiently lower when the meal is given orally than those obtained by feeding through gastrostomy.⁹ However, reflex inhibition is not the only factor involved, for considerable filling without significant increase of intragastric pressure may occur solely because of the physical relations involved.³¹

Much evidence indicates that food (especially fluids) passes preferentially along the gastric pathway (*Magenstrasse*). The inference that this scraping of food against the mucosa involves some trauma to the mucosa has been suggested as an explanation for the presence in this region of approximately 90 per cent of gastric ulcers,³² but the idea has not been universally supported by the more recent roentgen studies.

The food in the stomach is held chiefly in the "hopper" (body and fundus). Here it undergoes but little mixing, so that the portions tend to persist for some time as discrete layers, arranged concentrically as ingested. This material is gradually liquefied; the fats melt, the proteins are attacked by pepsin and hydrochloric acid, and the starch is partially digested by ptyalin. The entire mass is subjected to moderate pressure due to the persistent tone in this region and to infrequent feeble peristaltic waves. Periodically, a portion of the mass is forced into the "mill"

Stenosis, Pylorospasm and Chronic Vomiting (Merycism), *ibid.* **39**:310 (Jan.) 1916. (c) Ivy, A. C.: Contributions to the Physiology of the Stomach: LII. Studies on Gastric Ulcer, *Arch. Int. Med.* **25**:6 (Jan.) 1920.

29. Wolfer, J. A.: Chronic Ulcer of the Stomach: Its Experimental Production and Effect on Gastric Secretion and Motility, *Ann. Surg.* **81**:89 (Jan.) 1925.

30. (a) Gianturco, C.: Some Mechanical Factors of Gastric Physiology: Empty Stomach and Its Various Ways of Filling; Pressure Exerted by Gastric Walls on Gastric Content; Physical Changes Occurring to Foodstuffs During Digestion, *Am. J. Roentgenol.* **31**:735 (June) 1934. (b) Brody and others.⁹

31. Grey, E. G.: Observations on the Postural Activity of the Stomach, *Am. J. Physiol.* **45**:272 (Feb.) 1918.

32. Aschoff, L.: Lectures in Pathology, New York, Paul B. Hoeber, 1924, p. 365.

(pyloric antrum) where it is mixed and broken up into fragments by powerful peristaltic waves which pass toward the sphincter. The contractions starting near the incisura require approximately thirty seconds to reach the pylorus. Those starting near the cardia require one to three minutes to reach the pylorus. From one to four waves can be seen on the stomach at one time during gastric evacuation.

Fluids usually begin to leave the stomach promptly (between one and four minutes after ingestion), but more solid material makes its first appearance in the duodenum after a longer period. The factors governing this early evacuation are not definitely known, but in general, materials which might be irritating to the duodenum are retained and modified to make them more acceptable. According to recent observations made in this laboratory, the normal course of events proceeds according to the following pattern: A small portion of gastric contents enters the intestine. If the sample proves satisfactory, the remainder leaves the stomach rapidly; unsuitable material initiates reactions from the duodenum which temporarily retard further gastric evacuation.

The rate of gastric evacuation is largely determined by the antral tonus, the antral contraction waves, the activity of the pyloric sphincter and the character of the food. The belief that gastric emptying is dominated chiefly by a stopcock action of the pyloric sphincter has been presented so thoroughly elsewhere³³ that it will not be repeated here. However, it should be emphasized that this concept was based largely on indirect evidence. Theoretic considerations and more direct observations by Thomas³⁴ of the factors involved tended to place antral activity as the chief factor in normal evacuation. In trained dogs, Meschan and Quigley³⁵ observed the rhythmic passage of peristaltic waves in a comparatively uniform cycle over the antrum, the sphincter and the duodenal bulb. These three portions of the alimentary canal were found to respond almost invariably in a similar manner to factors which changed their tone and motility.

Subsequent studies by Werle, Brody, Ligon, Read and Quigley³⁶ confirmed these observations and showed that evacuation occurred when a propulsive peristaltic contraction wave involved the distal part of the

33. Murlin, J. R.: The Emptying Mechanism of the Stomach, *J. Nutrition* **2**: 311 (Jan.) 1930. Alvarez, W. C.: *An Introduction to Gastro-Enterology*, New York, Paul B. Hoeber, Inc., 1940.

34. Thomas, J. E.: Some Physical and Physiological Factors Involved in the Regulation of Gastric Emptying, *Rev. Gastroenterol.* **2**:32 (March) 1935.

35. Meschan, I., and Quigley, J. P.: Spontaneous Motility of the Pyloric Sphincter and Adjacent Regions of the Gut in the Unanesthetized Dog, *Am. J. Physiol.* **121**:350 (Feb.) 1938.

36. Werle, J. M.; Brody, D. A.; Ligon, E. W., Jr.; Read, M. R., and Quigley, J. P.: The Mechanics of Gastric Evacuation, *Am. J. Physiol.* **131**:606 (Jan.) 1941.

antrum and a positive pressure gradient obtained from the antrum to the duodenal bulb. Direct methods of observation indicated that the sphincter probably did not exercise the dominant control of evacuation, especially since it was in a position which could retard evacuation for only one third to one fourth of each cycle. Further, the sequential relation of the sphincter contractions to the antral and bulbar contractions actually indicates that the sphincter is much more effective in preventing duodenal regurgitation than in blocking gastric evacuation.

These recent studies indicate that gastric evacuation is determined chiefly by the action of the antral pump, i. e., the antral and bulbar pressure gradient, the degree of antral tone and the depth of antral peristalsis and whether the waves persist or tend to die out as they approach the sphincter. When the antral wave travels to the sphincter and completely occludes the lumen as it progresses, practically all material distal to the antral peristaltic wave is expelled; but when these conditions do not obtain, the major portion returns to the body of the stomach. The situation is further modified by the fact that the portion expelled is chiefly the thinner material; larger lumps are retained for further fragmentation. During most of the evacuation period, the peristaltic waves begin in the region of the incisura angularis, but as the period nears its termination, the waves originate higher in the gastric body and are effective in the expulsion of the last portion of chyme.

Stretching of the gastric wall by a large balloon or by the ingestion of food exaggerates the evacuating motility of the sphincter region,³⁷ and the studies of Van Liere³⁸ showed that the evacuation rate of a large meal is greater than that of a smaller meal. Significant distention of the stomach, such as that which follows the ingestion of large meals, would be contraindicated in patients with ulcer since the augmented evacuation drive would involve greater trauma to the region of the ulcer.

As the stomach discharges, however, influences are initiated from the proximal part of the intestine which tend to suppress gastric motility and check evacuation. The presence of an excessive quantity of an indifferent substance, such as Ringer's solution, in the duodenum or of small quantities of more specific substances, such as fats,¹⁰ hydrochloric acid,³⁹ protein split products,⁴⁰ sugars⁴¹ or hypertonic solutions,⁴² causes

37. Quigley, J. P.; Werle, J. M.; Ligon, E. W., Jr.; Read, M. R.; Radzow, K. H., and Meschan, I.: The Influence of Fats on the Motor Activity of the Pyloric Sphincter Region and on the Process of Gastric Evacuation Studied by the Balloon-Water Manometer and by the Optical Manometer-Fluoroscopic Technic, *Am. J. Physiol.* **134**:132 (Aug.) 1941.

38. Van Liere, E. J.; Sleeth, C. K., and Northup, D.: The Relation of the Size of the Meal to the Emptying Time of the Human Stomach, *Am. J. Physiol.* **119**:480 (July) 1937.

39. (a) Read, M. R.; Radzow, K. R.; Meschan, I.; Werle, J. M., and Quigley, J. P.: To be published. (b) Thomas, J. E.; Crider, J. O., and Mogan, C. J.:

more or less complete inhibition of the entire region of the sphincter—the antrum, the sphincter and the bulb. The antrum is the most profoundly inhibited structure of these three. (A transient period of augmented activity of the bulb and the sphincter may occur while the material is being expelled from the bulb.) Inhibition of the region of the sphincter results from a reflex (the enterogastric reflex) and the action of an inhibitory hormone (enterogastrone) originating in the duodenum. Thus, the presence of significant quantities of these substances in the chyme discharged into the duodenum suppresses the antral evacuating drive (propulsive peristalsis), delays evacuation and frequently decreases gastric secretion.⁴³

This “autoregulation” of the rate and the character of the material evacuated deserves considerable emphasis, since through its operation much chemical and mechanical trauma to the region of the sphincter is avoided. No doubt the mechanism is significant in reducing the tendency of ulcers to form or in permitting them to heal. Advantage is taken of this principle to suppress gastric motor and secretory activity in the clinical management of ulcer by employing frequent feedings with especial emphasis on a diet high in fat. This is exemplified by the routine care of ulcer advocated by Sippy and in the early feeding after ulcer hemorrhage emphasized by Meullengracht. Depression of gastric motor and secretory activity by the administration of enterogastrone extracted from the intestinal mucosa has been successfully employed to prevent experimental gastrojejunal ulcer.⁴⁴ It is not definitely known how the presence of peptic ulcer modifies the autoregulation mechanism or the role which modifications of this mechanism may have in the production or maintenance of an ulcer, but these problems should be investigated.

A Study of Reflexes Involving the Pyloric Sphincter and Antrum and Their Role in Gastric Evacuation, *Am. J. Physiol.* **108**:683 (June) 1934.

40. Thomas, J. E., and Crider, J. O.: Inhibition of Gastric Motility Associated with the Presence of Products of Protein Hydrolysis in the Upper Small Intestine, *Am. J. Physiol.* **126**:28 (May) 1939.

41. Quigley, J. P., and Phelps, K. R.: The Mechanism of Gastric Motor Inhibition from Ingested Carbohydrates, *Am. J. Physiol.* **109**:133 (July) 1934.

42. Gershon-Cohen, J.; Shay, H., and Fels, S. S.: Experimental Studies on Gastric Physiology in Man: Influence of Osmotic Pressure Changes of Salt and Sugar Solutions on Pyloric Action and Gastric Emptying in Normal and Operated Stomach, *Am. J. Roentgenol.* **40**:335 (Sept.) 1938.

43. Kosaka, T., and Lim, R. K. S.: Demonstration of the Humoral Agent in Fat Inhibition of Gastric Secretion, *Proc. Soc. Exper. Biol. & Med.* **27**:890, 1930. Kosaka, T.; Lim, R. K. S.; Ling, S. M., and Liu, A. C.: On the Mechanism of the Inhibition of Gastric Secretion by Fat: A Gastric-Inhibitory Agent Obtained from the Intestinal Mucosa, *Chinese J. Physiol.* **6**:107 (Feb. 15) 1932.

44. Hands, A. P.; Fauley, G. B.; Greengard, H., and Ivy, A. C.: Prevention of Experimental Gastrojejunal Ulcer by Enterogastrone, *Am. J. Physiol.* **133**:P314 (June) 1941.

In an attempt to reduce trauma in the pyloric region, sectioning of the vagi has been suggested as a method of treating peptic ulcer⁴⁵ or vagotonia.⁴⁶ Knowledge of the effects of vagotomy on the gastric motor and secretory activity of animals is still rather incomplete, and with regard to man the situation is even less satisfactory. Therefore this procedure should be undertaken with caution. From what is known in this field, it may be stated that vagotomy may have the desirable effect of eliminating gastric secretion induced reflexly over the vagi but that the response to a test meal would remain normal.⁴⁷ Decreased motor drive would develop,⁴⁸ the initial evacuation of fluids might be hastened, but the time required for complete evacuation of solids would be delayed. Some stagnation of the gastric contents, especially particulate matter, might occur, and this would be undesirable since prolongation of the contact of food with gastric mucosa would exaggerate the gastric phase of gastric secretion, and gastric juice of high acid concentration would collect. Vagotomy does not modify the normal sequential relation of contraction waves over the antrum, the sphincter and the bulb or produce a significant relaxation of this region in the dog.⁴⁹ The more undesirable effects of vagotomy would involve a suppression of the enterogastric reflex⁵⁰ and a modification of enterogastrone activity so that auto-regulation of gastric activity from the intestine would be practically eliminated. Beazell and Ivy⁵⁰ observed that chronic gastric ulcer followed bilateral vagotomy in the rabbit and less frequently in the dog when these were fed a rough diet. Marked histologic and functional changes were noted after vagotomy by Lasowsky and Ptschelina,⁵¹ while Best and Orator⁵² considered vagotomy of little value in the treatment of peptic ulcer.

45. Winkelstein, A., and Berg, A. A.: Vagotomy Plus Partial Gastrectomy for Duodenal Ulcer, *Am. J. Digest. Dis.* **5**:497 (Oct.) 1938. Mayo, C. H.: Division of the Vagi for Pylorospasm, *Ann. Surg.* **88**:669 (Oct.) 1928.

46. Barron, L. E., and Curtis, G. M.: Effect of Vagotomy on Gastric Motor Mechanism of Man, *Arch. Surg.* **34**:1132 (June) 1937.

47. Ferguson, J. H.: Effects of Vagotomy on Gastric Functions of Monkeys, *Surg., Gynec. & Obst.* **62**:689 (April) 1936.

48. Meek, W. J., and Herrin, R. C.: Effect of Vagotomy on Gastric Emptying Time, *Am. J. Physiol.* **109**:221 (Aug.) 1934.

49. Quigley, J. P., and Meschan, I.: The Role of the Vagus in the Regulation of the Pyloric Sphincter and Adjacent Portions of the Gut, with Especial Reference to the Process of Gastric Evacuation, *Am. J. Physiol.* **123**:166 (July) 1938.

50. Beazell, J. M., and Ivy, A. C.: Chronic Gastric Ulcer Following Bilateral Vagotomy in Rabbit and in Dog, *Arch. Path.* **22**:213 (Aug.) 1936.

51. Lasowsky, J. M., and Ptschelina, A. N.: Ueber trophische Magenstörungen unter der Einwirkung beiderseitiger Vagotomie, *Experimentelle morphologische Untersuchung*, *Virchows Arch. f. path. Anat.* **285**:755, 1932.

52. Best, R. R., and Orator, V.: Vagus Nerve and Its Relation to Peptic Ulcer, *Ann. Surg.* **96**:184 (Aug.) 1932.

STAGNATION OF GASTRIC CONTENTS

As gastric juice is normally secreted, it has an acidity of approximately 0.5 per cent.⁵³ This exceeds the acidity usually found for gastric contents (0.1 per cent hydrochloric acid or less), because under physiologic conditions gastric juice is neutralized and diluted: (1) by swallowed food, water and saliva; (2) by the secreted mucus, especially of the pyloric antrum, and (3) by regurgitated duodenal contents.

The studies of Boldyreff⁵⁴ and subsequent investigators showed that regurgitation of alkaline duodenal contents ordinarily occurs when the acidity of the gastric contents is excessive. This results in a dilution and neutralization of gastric acid with a consequent decrease in acidity to the normal range.

Dragstedt⁵⁵ and others presented evidence indicating that gastric contents approaching the composition of the pure secretion of the gastric glands (i. e., having a hydrochloric acid concentration in excess of 0.15 per cent) will digest the normal gastric wall. Thus it may be assumed that interference with either gastric evacuation or regurgitation can produce stagnation, hyperacidity and, finally, peptic ulcer. Hurst⁵⁶ observed an increase in volume and acidity of gastric juice in 60 per cent of a group of patients with ulcer, and in general the clinical data substantiates the view that gastric hyperacidity is commonly associated with ulcer, but it is frequently a debatable point whether the hyperacidity is the cause or the result of the ulcer.

Certain types of stagnation exaggerate and prolong gastric motility and gastric secretion; this favors production and maintenance of ulcer. Experimental stagnation of gastric contents was produced by folding the anterior wall of the stomach to produce an hourglass effect (Baggio). This resulted in lesions ranging from simple erosion to typical ulcer. Slocomb⁵⁷ made a partial obstruction of the duodenum of dogs and subsequently observed inflammatory changes and multiple ulcers. Fre-

53. Hollander, F.: The Composition of Pure Gastric Juice, *Am. J. Digest. Dis. & Nutrition* **1**:319 (July) 1934; *Studies in Gastric Secretion: V. The Composition of Gastric Juice as a Function of Its Acidity*, *J. Biol. Chem.* **104**: 33 (Jan.) 1934. Carlson.²

54. Boldyreff, W.: The Self-Regulation of the Acidity of the Gastric Contents and the Real Acidity of the Gastric Juice, *Quart. J. Exper. Physiol.* **8**:1, 1915.

55. Dragstedt, L. R.: Some Physiological Principles Involved in Surgical Treatment of Gastric and Duodenal Ulcer, *Ann. Surg.* **102**:563 (Oct.) 1935.

56. Hurst, A. F.: Scharstein Lecture on Precursors of Carcinoma of the Stomach, *Lancet* **2**:1023 (Nov. 16) 1929.

57. Slocomb, L. H.: Experimental Gastroduodenal Ulcer Produced by Partial Obstruction of the Duodenum, *J. Missouri M. A.* **24**:351 (Aug.) 1927.

quently, ulcer has been associated with the stagnation produced by a diaphragmatic hernia.⁵⁴

Steinberg and Starr⁵⁹ prevented spasm in the first part of the jejunum of Mann-Williamson dogs when they stripped the muscularis from the jejunum at its anastomosis with the stomach. Ulcer was subsequently absent from the stripped region but readily formed at the first portion of the jejunum having an intact muscle. Fauley and Ivy⁶⁰ repeated the experiment with a modified technic. Although the previous studies were not invalidated, these investigators demonstrated that a local spasm in the jejunum was not essential to the production of ulcer near the anastomosis. Inhibition of gastric motility may result from emotional stress, and the resulting stagnation of strong gastric juice may be a factor in the causation of ulcers ascribed to nervousness, worry and other emotional states.⁶¹

Gastric retention resulting clinically from interference with normal gastric evacuation or regurgitation is generally considered as an important factor in the maintenance of ulcer. This stagnation has been ascribed to functional abnormalities of the sphincter—pylorospasm or absence of normal relaxation, achalasia—or to pyloric cicatrization.⁶² Although spasms in the vicinity of an ulcer are common, they usually disappear under therapy, but cicatrization follows. Unless the spasm or scarring is extensive or involves adhesions which distort the viscus, they are usually not important from the motor standpoint.⁶³

58. Harrington, S. W.: Diaphragmatic Hernia Associated with Traumatic Gastric Erosion and Ulcer, *Surg., Gynec. & Obst.* **51**:504 (Oct.) 1930. Truesdale, P. E.: Gastric Ulcer Associated with Diaphragmatic Hernia, *New England J. Med.* **207**:385 (Sept. 1) 1932.

59. Steinberg, M. E., and Starr, P. H.: The Factor of Spasm in the Etiology of Peptic Ulcers, *Arch. Surg.* **29**:895 (Dec.) 1934.

60. Fauley, G. B., and Ivy, A. C.: The Factor of Spasm in the Etiology of Jejunal Ulcer, *Am. J. Digest. Dis. & Nutrition* **4**:160 (May) 1937.

61. Rivers, A. B.: Clinical Consideration of Etiology of Peptic Ulcer, *Arch. Int. Med.* **53**:100 (Jan.) 1934. Todd, T. W.: Behavior Patterns of the Alimentary Tract, Baltimore, Williams & Wilkins Company, 1930.

62. Lahey, F. H.: Treatment of Gastric and Duodenal Ulcer, *J. A. M. A.* **95**:313 (Aug. 2) 1930. Ivy, A. C., and Fauley, G. B.: Factors Concerned in Determining Chronicity of Ulcers in Stomach and Upper Intestine: Susceptibility of Jejunum to Ulcer Formation; Effect of Diet on Healing of Acute Gastric Ulcer, *Am. J. Surg.* **11**:531 (March) 1931. Hurst, A. F.: Alvarez Lecture on Unity of Gastric Disorders, *Brit. M. J.* **2**:89 (July 15) 1933. Miller, R. H.: Present-Day Review of Gastric and Duodenal Ulcer, *New England J. Med.* **206**:925 (May 5) 1932. Hughson, W.: Reflex Spasm of the Pylorus and Its Relation to Diseases of the Digestive Organs, *Arch. Surg.* **11**:136 (July) 1925. Wolfer, J. A.: Chronic Experimental Ulcer of the Stomach: Its Clinical Significance, *J. A. M. A.* **87**:725 (Sept. 4) 1926. Ivy.^{28c}

63. Jordan, S. M.: Review of Gastric Ulcer Problem, *J. A. M. A.* **107**:1451 (Oct. 31) 1936.

Various surgical procedures involving gastroenterostomy or pyloroplasty have been employed in the attempt to restore the physiologic relations by overcoming stagnation and also permitting the return of intestinal contents to the stomach. Frequently, these measures have failed to produce clinical relief. In many cases, this was related to the fact that interference with free communications between the stomach and the intestine did not obtain preoperatively. Clinical signs of pylorospasm or achalasia are based almost entirely on indirect observations and therefore are frequently misleading, but patients exhibiting definite functional or anatomic pyloric obstruction may anticipate improvement from suitable surgical intervention.

It is generally believed that the presence of hyperacidity produces pylorospasm and thus sets up a vicious circle. This theory may be questioned since it was based on indirect evidence which indicated that acid in the duodenum caused firm closure of the pyloric sphincter. Thomas, Crider and Mogan^{39b} and Read, Ligon, Meschen and Quigley^{39a} showed by direct methods that hydrochloric acid in the duodenum of the normal dog in concentrations similar to or even exceeding that of chyme does not produce pylorospasm. In fact, the predominant effect is inhibition of the entire region of the sphincter. When injected into the duodenal bulb, hydrochloric acid moderately increases rhythmic contractions of the sphincter for a brief interval, but this is followed by a relaxation of the entire region of the sphincter. Ulcer in close proximity to the sphincter is generally believed to produce pylorospasm, but since this theory also is based on indirect evidence, it should be accepted with reserve until substantiated by more direct evidence.

MECHANICAL TRAUMA

Trauma to the digestive tract is not essential to the formation of ulcer. However, in many cases trauma appears to be a contributing factor or occasionally even the major factor in the development and maintenance of ulcer. This is emphasized by the fact that the marked pressure changes associated with vomiting may readily produce gastric hemorrhage or ulceration. It was previously mentioned that trauma resulting from the scraping of material along the gastric pathway (*Magenstrasse*) tends to explain the high incidence of ulcer in that region. It is significant also that experimental lesions produced in this region heal more slowly than those along the greater curvature. Mann and Bollman⁶⁴ observed that experimental ulcers produced by toxic factors are almost always in the pathway of the outflow of gastric contents.

64. Mann, F. C., and Bollman, J. L.: Experimentally Produced Peptic Ulcers: Development and Treatment, *J. A. M. A.* **99**:1567 (Nov. 5) 1932. Mann, F. C.: Mechanism of Peptic Ulceration: Review of Results of Experimental Investigation, *Brit. M. J.* **1**:707 (April 8) 1939.

Also related to this trend of thought is the fact that a diet of coarse food increases the incidence of ulcer in an Eck fistula or in bilaterally vagotomized animals. Fauley and Ivy⁶⁵ delayed the healing of experimental ulcers by feeding food containing much roughage. Ulcers were produced in prematurely weaned calves by Konjetzney and Puhl⁶⁶ by feeding rough food. The calves, however, were poorly nourished, and this fact introduced an additional factor into the investigation but did not invalidate the experiments.

It has been observed both clinically and experimentally that when gastric contents are expelled in such a manner that they strike a region with some force, an ulcer may be induced or, if already present, may fail to heal. In dogs prepared by the Mann-Williamson⁶⁷ technic and observed by Mann and Bollman,⁶⁴ the site of the formation of ulcer is typical, constant and within limits can be modified. Normally, the ulcer forms 1 to 2 cm. distal to the point of exit of the gastric contents and in the area where the material strikes first and with the greatest force. After the ulcer is formed, if the jejunal segment leaving the stomach is made to continue in the same direction as the pylorus for several inches and then bend sharply, the first ulcer, relieved from the major mechanical trauma (although exposed to the same chemical environment), heals, while a second ulcer will form at the intestinal bend. Restriction of the opening between the stomach and the intestine to produce a nozzle effect causes the ulcer to develop and perforate more rapidly. On the contrary, if the propulsive force of the stomach is decreased by surgically producing an hourglass defect in the prepyloric region, the rate of the formation of ulcer is decreased. Morton⁶⁸ produced duodenitis (probably a precursor to the formation of ulcer) by encircling the pylorus with a constricting band of jejunal muscle.

A significant contribution by Mann and Bollman to the ulcer problem does much to explain and correlate the observations just mentioned and others of a similar nature. The first step in the process of ulcer healing, according to them, consists of the formation of a delicate membrane over the ulcer. This film is readily removed by a variety of mechanical or chemical factors, and the healing process then remains practically in abeyance during the gradual process of forming a new membrane.

The fact that mechanical trauma to the mucosa is significant in the genesis and the maintenance of peptic ulcer is further supported by a

65. Fauley, G. B., and Ivy, A. C.: Experimental Gastric Ulcer: Effect of Consistency of Diet on Healing, *Arch. Int. Med.* **46**:524 (Sept.) 1930.

66. Konjetzney, G. E., and Puhl, H.: Das sogenannte Ulcus pepticum des Magens der Absatzkälber, *Virchows Arch. f. path. Anat.* **262**:615, 1926.

67. Mann, F. C., and Williamson, C. S.: The Experimental Production of Peptic Ulcer, *Ann. Surg.* **77**:409 (April) 1923.

68. Morton, C. B.: Peptic Ulcer: Chronic Lesions of Duodenum Following Experimentally Produced Pyloric Dysfunction, *Arch. Surg.* **28**:467 (March) 1934.

variety of observations. The trauma incident to the presence of foreign bodies in the stomach was reported by Wheeler,⁶⁹ Eusterman and Mayo,⁷⁰ Schulze,⁷¹ Balfour and Good⁷² as a cause of chronic ulceration. Further, a portion of the success attendant on the use in ulcer therapy of bland or mucilaginous substances (mucin⁷³ and okrin⁷⁴) is related to their capacity to decrease trauma in the area of the ulcer. Fauley and Ivy⁷⁵ considered the prevention of postoperative jejunal ulcer by the use of bland diets and fundusectomy.

The impression is current that successful therapy of ulcer involves reducing the motor drive of the stomach, keeping the pyloric sphincter patent and promoting gastric evacuation. Pituitary extract reduces the tone and the motility of the stomach,⁷⁶ and this action may contribute to the favorable results claimed for this substance in the treatment of ulcer.⁷⁷ Alkalis, such as sodium bicarbonate, have enjoyed extensive employment in ulcer therapy, partially because these substances hasten gastric evacuation.⁷⁸ However, according to Meschan and Quigley,⁷⁹ this augmented evacuation is not without serious clinical objections since it results from an increased gastric motor drive and occurs in spite of increased activity of the pyloric sphincter.

69. Wheeler, P. H.: Enormous Benign Gastric Ulceration Caused by Multiple Foreign Bodies, *New England J. Med.* **214**:830 (April 23) 1936.

70. Eusterman, G. B., and Mayo, J. G.: Traumatic Peptic Ulcer, *Am. J. Surg.* **26**:74 (Oct.) 1934.

71. Schulze, V. E.: Persimmon Bezoar, with Report of a Case, *South. M. J.* **25**:833 (Aug.) 1932.

72. Balfour, D. C., and Good, R. V.: Phytobezoar Associated with Gastric Ulcer: Especial Reference to Persimmon Bezoar with Report of a Case, *Am. J. Surg.* **6**:579 (May) 1929.

73. Fogelson, S. J.: Treatment of Peptic Ulcer with Gastric Mucin: Preliminary Report, *J. A. M. A.* **96**:673 (Feb. 28) 1931; Gastric Mucin Treatment for Peptic Ulcer: Report on Questionnaires, *Arch. Int. Med.* **55**:7 (Jan.) 1935.

74. Jones, K. K.; Ivy, A. C., and Atkinson, A. J.: Treatment of Peptic Ulcer with Okrin: Preliminary Report, *Illinois M. J.* **63**:377 (April) 1933. Meyer, J.; Sidmon, E. E., and Necheles, H.: Treatment of Peptic Ulcer with Powdered Okra, *Illinois M. J.* **64**:339 (Oct.) 1933.

75. Fauley, G. B., and Ivy, A. C.: Prevention of Postoperative Jejunal Ulcers by Diet and Fundusectomy: Experimental Study in Dogs, *Surg., Gynec. & Obst.* **63**:717 (Dec.) 1936.

76. Quigley, J. P., and Barnes, B. O.: Action of Insulin on the Motility of the Gastro-Intestinal Tract: VI. Antagonistic Action of Posterior Pituitary Lobe Preparations, *Am. J. Physiol.* **95**:7 (Oct.) 1930.

77. Metz, M. H., and Lackey, R. W.: Peptic Ulcer Treated by Posterior Pituitary Extract, *Dallas M. J.* **24**:46 (April) 1938; Gastric Lesion Produced by Posterior Pituitary Extract, *Texas State M. J.* **34**:214 (Aug.) 1938.

78. Van Liere, E. J., and Sleeth, C. K.: The Emptying Time of the Normal Human Stomach as Influenced by Acid and Alkali, with a Review of the Literature, *Am. J. Digest. Dis.* **7**:118 (March) 1940.

79. Meschan, I., and Quigley, J. P.: To be published.

PERFORATION OF ULCER

As the depth of the erosion of peptic ulcer increases, the ease of perforation usually increases. Generally, the actual perforation results from an intragastric pressure greater than the intra-abdominal pressure, and this pressure gradient is always essential to the escape of gastric contents into the peritoneal cavity. Until accurate determinations have been made simultaneously within and outside the gastrointestinal wall under a variety of conditions, many important details regarding the mechanism of perforation must remain obscure. However, the essential pressure gradient and the resulting perforation apparently may develop from the weight of a column of gastric contents, loading the stomach with a large meal, vigorous gastric or duodenal contractions, manipulation or nonpenetrating trauma to the abdomen.⁸⁰ Hemorrhage from an ulcer or perforation of an ulcer apparently is rarely the direct result of physical exertion.⁸¹ Straining and similar exertion produces a general increase of intra-abdominal pressure, but this apparently cannot directly cause rupture. In respect to the effects of physical exertion on the pressures developed by the stomach itself, it has been found that vigorous exercise produces an early decrease in gastric motility, but increased gastric motility usually is a delayed effect of hard work and an early effect of mild exercise.⁸²

OPERATION IN THE REGION OF THE PYLORIC SPHINCTER

Surgical treatment of an ulcer is usually avoided except in cases of severe pyloric obstruction, intractable hemorrhage, perforation or ulcer repeatedly demonstrated not to be ameliorated by the standard medical management. When recourse to operation appears warranted, procedures

80. Corlette, C. E.: Trauma in Relation to Organic Visceral Disease, *M. J. Australia* **2**:587 (Nov. 7) 1931. Paas, H. R.: Ueber die Magen- und Duodenal-perforation nach Röntgen-Kontrastmahlzeit und ihre Folgen, *Deutsche Ztschr. f. Chir.* **247**:461, 1936.

81. Meyer, K. A., and Brams, W. A.: Acute Perforation of Gastric and Duodenal Ulcer, *Am. J. M. Sc.* **171**:510 (April) 1926. White, F. W.: The Etiology and Pathology of Perforating Gastric and Duodenal Ulcers, *Boston M. & S. J.* **177**:555 (Oct. 18) 1917. Rhodes, G. K., and Collins, D. C.: Acute Perforated Peptic Ulcers: A Clinical Review of One Hundred and Fifty-Five Consecutive Patients Treated Surgically, *California & West. Med.* **39**:173 (Sept.) 1933. Beams, A. J.: Some Industrial Aspects of Acute Perforation and Hemorrhage of Peptic Ulcer, *Ohio State M. J.* **32**:130 (Feb.) 1936. Workmen's Compensation Acts: Perforation of Peptic Ulcer Allegedly Due to Strain, *Bureau of Legal Medicine and Legislation; Medicolegal Abstracts, J. A. M. A.* **106**:411 (Feb. 1) 1936.

82. Hellebrandt, F. A., and Tupper, R. H.: Studies on the Influence of Exercise on the Digestive Work of the Stomach: II. Its Effect on Emptying Time, *Am. J. Physiol.* **107**:355 (Feb.) 1934.

intended to eliminate the functional activity of the pyloric sphincter are commonly employed. Such operations are undoubtedly of value in many cases in that they remove serious interference with duodenal regurgitation⁸³ or hasten gastric evacuation and thus reduce the acidity and the volume of the gastric contents. These possible modifications do not always explain the beneficial effects of operation on ulcer, for relief is frequently obtained when the operative procedure is not followed by alteration in the gastric acidity or the evacuation rate.

In the presence of gross mechanical obstruction of the pylorus, operations designed to eliminate the functional activity of the sphincter can be depended on to shorten the gastric evacuation time. However, the time for complete evacuation generally returns only to the normal and most observers agree that gastric dumping is not the usual effect of such operations. Evacuation still requires a pressure gradient from the stomach to the intestine, and this probably cannot be supplied by gravity or respiratory movements as has been suggested. It is dependent on gastric peristaltic waves which develop pressure in the stomach adequate to expel its contents and also on intestinal waves which propel material along the intestine and prevent the development of excessive intestinal back pressure. Thus it has been demonstrated that if the pylorus is patent, even though partially obstructed, much of the gastric contents and especially the more solid material is discharged through the pylorus rather than through any artificial opening.⁸⁴ This is understandable, since a more effective expulsion pressure gradient can be developed at the sphincter than at any other portion of the stomach. Much of the material evacuated through the pyloric sphincter reenters the stomach through a gastroenterostomy stoma. Since this material reduces gastric acidity, the return of a moderate volume is desirable; but if the intestinal loop draining the stoma is obstructed, the gastric contents may travel in a vicious circle. This was noted especially by the pioneers with this operation.

After pyloroplasty in the cat, the early stage of gastric evacuation is more rapid than normal.⁸⁵ However, most investigators have found the time for complete evacuation essentially normal, and the various food substances known to retard evacuation (e. g., fats, hypertonic salt or sugar solutions) still exercise their characteristic delaying effect.

83. Deaver, J. B., and Burden, V. G.: Further Experience with Resection of Anterior Half of Pyloric Sphincter, *Ann. Surg.* **92**:533 (Oct.) 1930.

84. (a) Kelling, G.: Studien zur Chirurgie des Magens, *Arch. f. klin. Chir.* **62**:1, 1900. (b) Cannon, W. B., and Blake, J. B.: Gastro-Enterostomy and Pyloroplasty: An Experimental Study by Means of the Roentgen Rays, *Ann. Surg.* **41**:686, 1905.

85. Pannett, C. A.: An Experimental Investigation of the Results of Linear Division of the Pyloric Sphincter, *Brit. J. Surg.* **8**:262 (Jan.) 1921. Cannon and Blake,^{84b}

This has been demonstrated in the dog following pylorosection⁸⁶ after mechanically propping the sphincter open,⁸⁷ after sectioning the pyloric sphincter or producing a gastroenterostomy⁸⁸ and after Billroth I or Polya resections or gastroenterostomy.⁸⁹ Similar results have been demonstrated in human subjects by Case,⁹⁰ Gaither,⁹¹ Kirschner,⁹² Beresow and Stern.⁹³ Shay and Gershon-Cohen⁹⁴ reported moderate shortening of the evacuation time of barium sulfate and water in the human being after Billroth I or Polya resections, and food substances produced slightly less retardation than in patients on whom operation was not performed. Such a deviation from normal can be chiefly ascribed to the fact that the test substances were introduced into a lower section of the intestine, since it has repeatedly been demonstrated that the antral inhibition produced by the enterogastric reflex or by enterogastrone is

86. von Mering, J.: Ueber die Funktion des Magens, *Verhandl. d. deutsch. Cong. f. inn. Med.* **15**:433, 1897. Thompson, H. L.: Resection of Pylorus—Its Effect on Secretory and Motor Functions of Stomach, *California & West. Med.* **36**:383 (June) 1932. Medoff, J.; Neuwelt, F.; Patedjl, J., and Necheles, H.: A Study of the Functions of the Stomach Following Pyloric Obstruction and Gastrotomy, *Am. J. Physiol.* **133**:386 (June) 1941.

87. Crider, J. O., and Thomas, J. E.: A Study of Gastric Emptying with the Pylorus Open, *Am. J. Digest. Dis. & Nutrition* **4**:295 (July) 1937.

88. Crisler, G. R., and Van Liere, E. J.: Pyloroplasty, Gastroenterostomy, and Partial Parasympathetic Denervation of the Pyloric Sphincter, and Their Relation to the Emptying Time of the Stomach, *Am. J. Digest. Dis. & Nutrition* **3**:167 (May) 1936. Gianturco.^{30a}

89. Johnston, C. G., and Ravdin, I. S.: Action of Glucose on Emptying of Stomach: Effect of Varying Concentrations in Both Normal Stomachs and After Various Gastric Operations, *Ann. Surg.* **101**:500 (Jan.) 1935. Ravdin, I. S.; Pendergrass, E. P.; Johnson, C. G., and Hodes, P. J.: Effect of Foodstuffs on Emptying Normal and Operated Stomach and Small Intestinal Pattern, *Am. J. Roentgenol.* **35**:306 (March) 1936. Tanaka, K.: Observations and Kinematographic Studies Through Korwaischen Fistulae of the Movements of Operated Stomachs and Intestines in Dogs and Cats, *Ztschr. d. jap. Chir. Gesellsch.* **36**:122, 1935.

90. Case, J. T.: Gastric and Duodenal Roentgen-Ray Findings After Operation, *J. A. M. A.* **85**:1385 (Oct. 31) 1925.

91. Gaither, E. H.: Effects of Surgery of the Stomach on Its Subsequent Motor and Secretory Functions, *J. A. M. A.* **91**:1075 (Oct. 13) 1928.

92. Kirschner, M., and Mangold, E.: Die motorische Funktion des Sphincter Pylori und des Antrum beim Hunde nach der queren Durchtrennung des Magens, *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* **23**:446, 1911; *Centralbl. f. Chir.* **56**:844, 1929.

93. Beresow, E., and Stern, N.: Die Arbeitsleistung des nach Billroth I operierten Magens, *Deutsche Ztschr. f. Chir.* **236**:465, 1932.

94. Shay, H., and Gershon-Cohen, J.: Experimental Studies in Gastric Physiology in Man: The Mechanism of Gastric Evacuation After Partial Gastrectomy as Demonstrated Roentgenologically, *Am. J. Digest Dis. & Nutrition* **2**:608 (Dec.) 1935.

elicited with much less intensity from portions of the intestine other than the proximal portion of the duodenum.

Schekhter⁹⁵ and others noted that evacuation is rhythmic after resection of the pylorus. This is due chiefly to the expulsion of material by rhythmic peristaltic waves of the stomach. The fact must also be considered that the sphincter function is not a unique property of the pylorus but is also possessed in some degree by antral muscle. This is indicated by the evidence presented by Meyer and Schmidt⁹⁶ that sphincter action may develop at any gastrointestinal anastomosis. From gastroscopic observations Schindler and Dailey⁹⁷ also concluded that the development of typical sphincter activity is a general property of any portion of the antrum. When observed by this technic, gastroenterostomy stomas usually remained gaping and motionless, but occasionally displayed sphincter action—rhythmically opening and closing in stellate fashion. The two sphincters did not uniformly act synchronously even when only a few centimeters apart. Cannon and Blake^{84b} and Case⁹⁰ ascribed the rhythmic discharge of gastric contents and the essentially normal evacuation rate observed after sectioning the pyloric sphincter to rhythmic contractions of muscle rings in the duodenum. Thus it is evident that elimination of the functional activity of the pyloric sphincter may influence the process of gastric evacuation but slightly, either because the normal influence of the sphincter on emptying is only moderate or because adjacent structures develop a vicarious sphincter action.

Results not in accord with those presented have been reported by several authors. After subtotal gastric resection, Strauss and associates⁹⁸ found the emptying time, the character of the hunger contractions and the size of the stomach subject to considerable variation. Review of the literature and personal observations led Vitkin⁹⁹ to conclude that resection of the stomach produced considerable change in the form, the tone and the topographic relations of the stomach. The stomach became feeble and distended; food was insufficiently macerated, mixed or digested and was evacuated too rapidly. Carty, Weintraub

95. Schekhter, I. A.: Form, Localization and Motor Function of the Stomach After Resection for Ulcer, *Novy Khir. Ark.* (no. 163) **41**:346, 1938.

96. Meyer, H., and Schmidt, W.: Der operierte Magen, *Ergebn. d. med. Strahlenforsch.* **4**:479, 1930.

97. Schindler, R., and Dailey, M. E.: Gastroscopic Observations on Gastric Motility, *Am. J. Digest. Dis.* **8**:8 (Jan.) 1941.

98. Strauss, A. A.; Strauss, S.; Lewitsky, P.; Schenan, L.; Seidon, E. E.; Arens, R. A.; Meyer, J., and Necheles, H.: Physiological and Clinical Studies of Patients After Subtotal Gastrectomy, *Am. J. Digest. Dis. & Nutrition* **4**:32 (March) 1937.

99. Vitkin, S. F.: Motor Functions of the Stomach After Resection, *Ann. Surg.* **111**:27 (Jan.) 1940.

and Felter¹⁰⁰ claimed that after gastroenterostomy, gastric resection or pyloroplasty, only those patients responded well whose stomach was smaller, higher, more lateral than normal and displayed diminished peristalsis and rapid evacuation. They considered return of vigorous gastric peristalsis, increase in the size of the stomach and reestablishment of gastric discharge through the sphincter as indications of failure of the operative procedure. The differences in opinion in this field here outlined result in part from variations in the surgical technic employed, as well as in the method and the time of observation following the surgical intervention.

According to Truesdale,¹⁰¹ Horwitz, Alvarez and Ascanio,¹⁰² the presence of gastric and duodenal ulcer results in hypertrophy of the pylorus, especially the sphincter, and consequently pyloric obstruction develops. They also presented evidence which indicates that gastroenterostomy leads to atrophy of the pyloric musculature. The edema due to trauma incident to anastomosis of the stomach and the intestine by Billroth I or II resection persists for only a short time, but Mecray, Barden and Ravdin,¹⁰³ Barden, Ravdin and Frasier,¹⁰⁴ Hoelzel and Da Costa¹⁰⁵ showed that hypoproteinemia, which is frequently present in patients subjected to such operations, produces edema of the stomach and inhibition of gastrointestinal motility parallel to the degree of hypoproteinemia. This may cause sufficient edema of the stoma to retard gastric evacuation greatly until the deficiency of protein is relieved.

SUMMARY

The normal and abnormal motor activities of the stomach and the proximal portion of the intestine which characterize hunger, gastric evacuation, duodenal regurgitation, hypermotility or hypomotility, spasm and stagnation have important relations to the ulcer problem. Hunger contractions or spasms involving the ulcer region are among the chief

100. Carty, J. R.; Weintraub, S., and Felter, R. K.: An X-Ray Study of the Post-Operative Stomach, *Radiology* **22**:191 (Feb.) 1934.

101. Truesdale, P. E.: The Pylorus: Observations on Its Musculature, *Surg., Gynec. & Obst.* **21**:298, 1915.

102. Horwitz, A.; Alvarez, W. C., and Ascanio, H.: The Normal Thickness of the Pyloric Muscle and the Influence on It of Ulcer, Gastroenterostomy and Carcinoma, *Ann. Surg.* **89**:521 (April) 1929.

103. Mecray, P. M., Jr.; Barden, R. P., and Ravdin, J. S.: Nutritional Edema: Its Effect on the Gastric Emptying Time Before and After Gastric Surgery, *Surgery* **1**:64 (Jan.) 1937.

104. Barden, R. P.; Ravdin, I., and Frasier, W. D.: Hypoproteinemia as Factor in Retardation of Gastric Emptying After Operations of Billroth I or II Types, *Am. J. Roentgenol.* **38**:196 (July) 1937.

105. Hoelzel, F., and Da Costa, E.: Experimental Production of Pylorospasm and Gastric Retention in Rats, *J. Exper. Med.* **57**:597 (April) 1933.

causes of ulcer distress. Trauma to susceptible portions of the intestine often is a factor in the production or the maintenance of an ulcer. Such trauma results from (1) scraping of the gastrointestinal contents against the mucosa and (2) projection of gastrointestinal contents against a particular area of the mucosa. These factors are aggravated by rough food, large meals, long intervals between meals or the production of a nozzle effect by narrowing the lumen, especially of the pyloric sphincter.

Gastric evacuation in health and in disease is apparently more dependent on the character of antral peristalsis and the antral and bulbar pressure gradient and less dependent on the activity of the pyloric sphincter than was indicated by earlier studies. Food in the upper intestine initiates the enterogastric reflex and liberates enterogastrone, thus checking gastric motor and secretory activity. This autoregulation of gastric evacuation reduces the motor drive during evacuation and by decreasing trauma to the area in which most ulcers develop must be significant in preventing the formation of ulcers or in permitting ulcers to heal.

Stagnation of gastric or intestinal contents usually stimulates motor and secretory activity, interferes with the normal dilution and neutralization of gastric juice and thus permits strongly acid material to accumulate. This type of gastric juice can digest even normal gastrointestinal mucosa and produce ulcers. Unless the pyloric sphincter is grossly obstructed, surgical procedures designed to circumvent the sphincter function usually exert but little influence on gastric evacuation.

PATHOGENESIS OF GASTRODUODENAL ULCER

LESTER R. DRAGSTEDT, M.D.

CHICAGO

The problem of the cause of gastric and duodenal ulcer is a part of the more general question of the resistance of the gastrointestinal tract to the digestive action of its own secretions. This was well stated in a thoughtful paper by Joseph Warren¹ more than fifty years ago:

. . . The question is: Why do organisms which manifest such power of digesting and assimilating the material they require, leave quite intact those organs or tissues where these processes go on so actively? Why does the stomach digest various albuminous substances so readily, and yet fail to attack its own walls, containing substantially the same material? Why do the intestines, with their much more varied power of digestive action, remain undisturbed and uninjured by this activity? Why does the pancreas secrete at least three vigorous ferments, and yet work on unaffected by each and all of them?

John Hunter² interested himself in this problem and explained the resistance of the normal gastric wall to digestion on the basis of a vital principle in the following picturesque language:

. . . If it was possible for an animal to live in the stomach of another animal, supposing digestion not to be going on in that stomach, it would then live while digestion was going on; for that animal would not be in the least dissolved, because the living principle in the animal would prevent or counteract the digestive quality of the stomach. If this was not the case then we might readily suppose that even though the animal life was not immediately affected by the digestive power, yet at last it might be destroyed by the external and extreme parts of the animal being digested, and so the animal be obliged to die, like a person with mortification. But that a living animal will not be so dissolved is every day proved by worms, maggots or flies, living in the stomach of many animals; and if it was a power that could act upon a part that had the living principle, as well as an acid can, then the stomach itself would certainly be dissolved. If one could conceive a man to put his hand into the stomach of a lion, and hold it there without hindering the digestive powers, the hand would not in the least be digested; and if the hand of a dead man was put in at the same time, whether separated or not from the body, that hand would be digested while the other would not.

From the time of Hunter many men have speculated and worked in this field, and the view has steadily gained headway that ulcer of the stomach is in some way due to a local loss of resistance on the part of

From the Department of Surgery of the University of Chicago.

1. Warren, J. W.: Boston M. & S. J. **116**:249, 1887.

2. Hunter, J.: *Essays and Observations on Natural History, Anatomy, Physiology, Psychology and Geology*, London, J. Van Vooret, 1861, vols. 1-2.

the mucous membrane to the digestant activity of the gastric juice. The widely adopted term "peptic ulcer" is an expression of that view. The occurrence of the lesion in those parts of the alimentary tract that are exposed to gastric juice (viz., the lower part of the esophagus, the stomach, the first portion of the duodenum, the part of the jejunum adjacent to a gastroenterostomy stoma and the part of the ileum adjacent to the entrance of Meckel's diverticulum when this contains gastric mucosa) and nowhere else may be taken as strong confirmatory evidence. However, under normal conditions the mucous membrane is not digested away.

During the past twenty years a great many significant experiments have been done and observations made that have helped to bring into view certain conditions under which chronic progressive ulcer in the stomach and intestines may be expected. As a direct result of planned experimental procedures the disease has been caused to develop in dogs, cats and rats and to duplicate in almost every particular that encountered in man. The gross and histologic appearance of the experimental ulcer exactly resembles the clinical lesion, and it has been observed to perforate, to cause profuse and fatal hemorrhage and to heal under a type of medical management which resembles that found effective in man. It seems likely therefore that an accurate understanding of the alterations in the physiology of the alimentary tract under which experimental ulcer forms and heals should largely clarify the clinical problem.

RESISTANCE TO THE DIGESTIVE ACTION OF THE NORMAL GASTRIC CONTENT BY THE GASTRIC AND THE DUODENAL MUCOSA

The chemical and mechanical traumas produced by the normal gastric content are not sufficient to induce lesions in the normal gastric and duodenal mucosa and prevent them from healing or indeed to delay materially the healing of extensive lesions artificially produced. The prompt healing of the gastric mucosa after the most extensive resections has been commented on by many authors. The earlier literature on ulcer is replete with more or less unsuccessful attempts to produce a chronic progressive lesion in the gastric or duodenal mucosa of the dog or the rabbit. Rapid healing has usually been found to take place when acute lesions of the stomach wall have been produced by the actual cautery, chemical corrosives, excision of large areas of mucosa, ligation or thrombosis of the gastric vessels and the local and intravenous injection of bacterial cultures. This effort has served, however, to make evident the great capacity of the gastric mucosa of these animals to heal in the presence of the usual gastric content even after the most extensive

mechanical and chemical traumas. Bolton,³ Friedman and Hamburger,⁴ Dragstedt and Vaughn,⁵ Shapiro and Ivy,⁶ Wolfer⁷ and others have produced chronic gastric ulcers in dogs by methods which are chiefly serviceable in studying the subsequent effect of this type of trauma on the secretory and motor functions of the stomach but are of doubtful significance in determining the cause of the spontaneous lesions.

RESISTANCE TO THE DIGESTIVE ACTION OF THE NORMAL GASTRIC CONTENT BY OTHER ORGANS

Resistance to the digestive action of the normal gastric content is not limited to the gastric and the duodenal mucosa. As previously noted, Hunter expressed the opinion that all living uninjured cells could resist the digestive action of the gastric content—a statement that at the present time seems to be at least partially true. I⁵ have reviewed the earlier literature on this problem, and there is no need for repetition here. The experiments reported in my former paper have been confirmed and amplified in my laboratory in the succeeding years, and the following observations are well supported by numerous experiments. An isolated segment of the duodenum, the jejunum, the ileum or the colon of a dog may be successfully implanted into a defect in the stomach. If the transplant is made in such a way that the mesenteric blood supply is not interfered with and the mucous surface is exposed, the transplant will remain grossly intact and of normal appearance for at least a year; this is evidenced by the work of Fiori,⁸ Mann⁹ and Dragstedt and Vaughn.⁵ In a somewhat similar way the spleen, the kidney or the pancreas of a dog may be mobilized and sutured into a defect in the gastric wall. If this is done with care not to injure the blood supply of the transplant, it will remain undigested for many weeks. The fibrous capsule of the sutured organ may be first removed so that the gastric content has direct access to the parenchyma, and still the tissue is not digested away, but rather in time a thin layer of gastric mucosa grows out from the cut edge and finally covers the surface of the transplant.¹⁰

3. Bolton, C.: *Ulcer of the Stomach*, London, Edward Arnold & Co., 1913, p. 386.

4. Friedman, J. C., and Hamburger, W. W.: *Experimental Chronic Gastric Ulcer*, J. A. M. A. **63**:380 (Aug. 1) 1914.

5. Dragstedt, L. R., and Vaughn, A. M.: *Gastric Ulcer Studies*, Arch. Surg. **8**:791 (May) 1924.

6. Shapiro, P. F., and Ivy, A. C.: *Gastric Ulcer: Experimental Production of Gastric Ulcer by Local Anaphylaxis*, Arch. Int. Med. **38**:237 (Aug.) 1926.

7. Wolfer, J. A.: Ann. Surg. **84**:89, 1926.

8. Fiori, P.: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **26**:239, 1913.

9. Mann, F. C.: J. M. Research **35**:289, 1917.

10. Dragstedt, L. R.: Ann. Surg. **102**:563, 1935.

CAPACITY OF PURE GASTRIC JUICE TO DESTROY ALL LIVING TISSUES

Pure gastric juice has the capacity to destroy and digest all living tissues, including the wall of the stomach itself. A somewhat complicated type of experimental procedure has been required to secure the evidence for this statement. The usual gastric content consists of a mixture of swallowed food and saliva, gastric juice from the parietal cells of the fundus, mucus and a neutral or faintly alkaline secretion from the pyloric antrum and varying quantities of regurgitated duodenal juices. Pure fundus secretion can be obtained by constructing in a dog the Heidenhain or Pavlov accessory stomach pouch or one of the more recent modifications. Larger quantities may be obtained by isolating the entire stomach from continuity with the esophagus and duodenum, either with the vagi severed as in the method of Lim, Ivy and McCarthy¹¹ or with the vagus innervation preserved as described by Dragstedt and Ellis.¹² Juice is secreted by the isolated pouch or stomach as a result of secretory impulses carried by the vagus nerves where these persist and through the action of the gastric hormone, gastrin, liberated from the stomach or the upper intestine in response to the ingestion of food. The fundus secretion obtained in this way consists almost entirely of a water solution of hydrochloric acid and the enzyme pepsin.¹³ The hydrochloric acid is present in an almost constant concentration of about 135 clinical units.

Living tissues have been exposed to the digestant action of this pure undiluted secretion in various ways. Matthews and Dragstedt¹⁴ permitted the secretion from a small Heidenhain or a Pavlov pouch to drain into the jejunum or the ileum instead of to the outside and noted the development of a large progressive perforating ulcer in the intestinal mucosa adjacent to the anastomosis with the accessory stomach. When the implant was made into the ileum, ulcer developed in 100 per cent of the cases, but when the anastomosis was made with the jejunum, the incidence of ulcer was reduced to 85 per cent; this indicates perhaps a greater resistance of the more oral mucosa. In a similar experiment Goldberg¹⁵ prepared a Heidenhain pouch of the stomach and connected it to the exterior by means of a segment of small intestine. Ulcer appeared in the mucosa of the intestinal segment near the anastomosis with the accessory stomach.

Organs such as the spleen, the kidney, the pancreas, the omentum and the intestinal serosa may be subjected to the digestive action of pure

11. Lim, R. K. S.; Ivy, A. C., and McCarthy, J. E.: *Am. J. Physiol.* **74**:616, 1925.

12. Dragstedt, L. R., and Ellis, J. C.: *Am. J. Physiol.* **93**:407, 1930.

13. Hollander, F.: *J. Biol. Chem.* **104**:33, 1934.

14. Matthews, W. B., and Dragstedt, L. R.: *Surg., Gynec. & Obst.* **55**:265, 1932.

15. Goldberg, S. L.: *Ann. Surg.* **96**:155, 1932.

gastric juice by implanting them into defects in the walls of isolated Pavlov or Heidenhain accessory stomachs or in totally isolated stomachs. When this is done, the transplant becomes promptly excavated by the digestive action of the gastric juice, and death from hemorrhage takes place in a few days.¹⁰ The contrast with the almost complete immunity from digestion of such tissues implanted into similar defects in normal stomachs is striking and shows that pure gastric juice has a marked aggressive action on living tissue, while the gastric content is relatively inert.

The experimental ulcer in the lower intestine has its counterpart in the ulcer found in the ileum of man opposite the entrance of persisting Meckel's diverticulum. The diverticulum in these cases has been found to contain heterotopic gastric mucosa of the fundus type,¹⁶ and in a recent case in which I performed an operation a fluid acid to litmus was demonstrated in the excised specimen. It is thus certain that this misplaced gastric mucosa can secrete an acid juice, and it is highly probable that the secretion is identical in composition with that from the stomach.

In all of the experiments in which pure gastric juice from an isolated pouch of the stomach is permitted to flow into the lower intestine, the ulcer forms in the intestinal rather than in the gastric mucosa. Since the exposure is similar, one must conclude that the gastric mucosa has the greater resistance to digestion. That this protective capacity is not absolute has been demonstrated clearly by means of the completely isolated stomach in which the secretory vagus innervation has been preserved. Dogs prepared in this way have been under almost continuous observation in my laboratory for the past twelve years.¹² If the alkalosis and the dehydration incident to the total loss of gastric juice are compensated for by the intravenous injection of adequate salt solution, these animals may survive in good condition for many months. They secrete volumes of gastric juice ranging from 1,500 to 2,500 cc. in twenty-four hours with a free acid content of 130 to 140 clinical units and a high pepsin content. In the great majority a large sharply punched-out ulcer develops in the middle portion of the isolated stomach and causes profuse hemorrhage or perforates and produces rapidly fatal peritonitis. The development and the progress of gastric ulcer have been observed by introducing a cystoscope through the external cannula into the cavity of the stomach. The preservation of the secretory fibers of the vagus nerves to the isolated stomach seems to be a matter of some importance in the genesis of the ulcer since Ivy reported that in his extensive experience with the same preparation after the vagi have been severed, no ulcer was found.

16. Dragstedt, L. R.: *Ulcers Acidum of Meckel's Diverticulum*, J. A. M. A. **101**:20 (July 1) 1933.

WHY THE GASTRIC WALL IS NOT NORMALLY DIGESTED AWAY

Under normal conditions the gastric wall is not digested away because it is not exposed to pure gastric juice. This conclusion follows from a consideration of the experimental evidence just presented and of those factors which normally regulate the secretions of the stomach. Carlson¹⁷ found that the empty stomach of the average healthy young adult man when aspirated in the morning before breakfast contained usually less than 50 cc. of fluid, often bile stained and with no free acid or at most only slight amounts. The normal stimuli for gastric secretion, such as the sight, the odor and the taste of food, are followed so promptly by its ingestion that the secretion from the fundus is largely diluted and neutralized. The secretion of gastric juice dependent on the chemical mechanism occurs in response to the presence of food in the stomach or the upper intestine, and the rate of secretion falls off rapidly when the stomach becomes empty. It is thus evident that food, which in normal persons is the stimulus for the formation of gastric juice, is also the chief factor which protects the tissues against its corrosive activity.

A continuous secretion of gastric juice occurs which is apparently not dependent on psychic stimuli or the presence of food in the stomach. The volume of this secretion appears to be slight as compared with the large amounts called forth in response to the taking of food. While the initial acidity of this juice is probably comparable with that of the food-stimulated secretion, the small volume permits almost complete neutralization by the mucus of the pyloric antrum, swallowed saliva and possibly also regurgitated duodenal juices. It is conceivable that this neutralizing mechanism may fail or prove inadequate in various ways and that as a result more or less pure gastric juice may accumulate in the stomach empty of food. It seems probable that some abnormality of this type is responsible for most of the cases of ulcer in man.

FAILURE IN THE MECHANISM OF NEUTRALIZATION AS A CAUSE OF ULCER

Does a failure in the mechanism for the neutralization of gastric juice cause ulcer? As pointed out before, in healthy persons gastric juice appears to be secreted by the fundus mucosa at a constant acidity in the neighborhood of 135 clinical units. While food is probably the most important neutralizing factor, a considerable body of evidence has accumulated which indicates that other factors are important, and it is, of course, on these that the whole burden falls if excessive secretion occurs in the absence of the taking of food. The work of Mann and associates published in 1923¹⁸ must be credited largely with establishing

17. Carlson, A. J.: *Physiol. Rev.* **3**:1, 1923.

18. Mann, F. C., and Williamson, C. S.: *Ann. Surg.* **77**:409, 1923.

the importance of the neutralizing effect of the duodenal juices in preventing the development of ulcer in the duodenum. Mann and co-workers accomplished this by demonstrating that diversion of the bile, the pancreatic and the duodenal juice into the lower ileum by their procedure of internal duodenal drainage produced progressive perforating ulcers in the part of the intestine adjacent to the pylorus in 95 per cent of the cases. Before this work similar evidence had been presented by Exalto in 1911¹⁹ and Langenskiöld in 1913.²⁰ Mann's striking experiments stimulated a large number of studies on the relative importance of each of the three duodenal juices in this protective action. While most of this evidence falls in line with the concept that the effect can be attributed to the capacity of these secretions to neutralize the gastric acid, some apparently contradictory results have been obtained.

Effect of the Exclusion of Bile from the Upper Intestinal Tract.—Bile has been excluded from the duodenum in experimental animals by diverting it to the outside by various types of external fistula, by diverting it into the pelvis of the kidney, from which it passes out in the urine, by diverting it into the lower intestine or the colon, and by completely and permanently occluding the bile ducts.²¹ The results of these procedures with respect to the incidence of ulcer in the duodenum vary widely. Complete obstruction to the bile ducts with resultant jaundice and hepatic cirrhosis leads to the development of typical progressive ulcers in the duodenum in the great majority of animals so prepared. On the other hand, certain kinds of external biliary fistula may divert the bile from the duodenum for many months without causing ulceration. Thus during the past five years in my laboratory I have observed 15 dogs provided with total biliary fistulas survive for periods of six to fifteen months and at death display no evidence of ulcer in the stomach or the duodenum. In these animals the common bile duct was doubly ligated and divided, and a large gold-plated cannula was placed in the fundus of the gallbladder. This cannula was then carefully wrapped with part of the omentum and led outward through a stab wound in the abdominal wall. Bile was collected in rubber bags tied to the cannula. It is possibly of considerable importance that no obstruction to the free escape of bile exists with this type of fistula, that ascending infection does not occur and that the liver remains grossly and histologically

19. Exalto, J.: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **23**:13, 1911.

20. Langenskiöld, F.: Skandinav. Arch. f. Physiol. **31**:1, 1913.

21. Berg, B. N., and Jobling, J. W.: Biliary and Hepatic Factors in Peptic Ulcers: Experimental Study, Arch. Surg. **20**:997 (June) 1930. Andrews, E.: Personal communication to the author. Kapsinow, R.: Ann. Surg. **83**:614, 1926. Blanck, E. E.: Surg., Gynec. & Obst. **61**:480, 1935. Bollman, J. L., and Mann, F. C.: Peptic Ulcer in Experimental Obstructive Jaundice, Arch. Surg. **24**:126 (Jan.) 1932.

normal. It seems possible that the varying incidence of ulcer reported after external biliary fistula by the Rous and McMaster technic or after anastomosis of the gallbladder to the ileum, the colon or the pelvis of the kidney following occlusion of the common duct may be due in part to the factors of partial obstruction or ascending infection. The probability that damage to the liver is important in the genesis of some of these ulcers resulting from biliary fistula is further supported by the observations of Bollman and Mann²² that chronic duodenal ulcers occasionally appear in animals with Eck fistula as well as after the administration of cinchophen.²³ This question of the relation of damage to the liver to gastroduodenal ulcer should receive further study.

Effect of the Exclusion of Pancreatic Juice from the Upper Intestinal Tract.—Pancreatic juice has been excluded from the duodenum of the dog by various types of external pancreatic fistula, by the implantation of the ducts into the lower intestine, by ligation of the ducts and by total pancreatectomy. Here again the results vary widely. Partial exclusion of the pancreatic juice has been produced by a great many workers from the time of De Graaf by cannulating or implanting the lower, larger pancreatic duct of the dog into the abdominal wall. Ulcer in such animals rarely develops. When Elman²⁴ cannulated this duct by the Rous and McMaster method after first ligating the other ducts, he secured a much greater volume of pancreatic juice and observed ulcer in the duodenum.

The failure to obtain ulcer in the duodenum by producing an external fistula of the lower pancreatic duct in the dog is undoubtedly due to the fact that in this preparation the major portion of the pancreatic secretion still finds its way into the duodenum. This is illustrated by the occurrence of ulcer in almost 100 per cent of the animals from which the entire secretion is drained to the outside by the type of fistula described by Dragstedt, Montgomery and Ellis.²⁵ Since that report, more than a hundred such fistulas have been prepared in the laboratory in connection with various problems. The principle of the method has remained to produce an isolated sac of that small portion of the duodenum receiving the pancreatic ducts and to lead the juice from this sac to the outside by means of a gold-plated cannula wrapped in omentum. The continuity of the alimentary tract may be reestablished by end to end

22. Bollman, J. L., and Mann, F. C.: Chronic Duodenal Ulcer in Animals with Fistulas on Certain Diets, *Arch. Path.* **4**:492 (Sept.) 1927.

23. Stalker, L. K.; Bollman, J. L., and Mann, F. C.: *Am. J. Digest. Dis. & Nutrition* **3**:822, 1937.

24. Elman, R.: *J. Clin. Investigation* **10**:183, 1931.

25. Dragstedt, L. R.; Montgomery, M. L., and Ellis, J. C.: *Proc. Soc. Exper. Biol. & Med.* **28**:109, 1930.

anastomosis of the divided duodenum or by the method originally described. These animals die rapidly of dehydration and acidosis unless the sodium lost in the pancreatic juice is replaced by parenteral injection. When this is done, life is greatly prolonged, but almost inevitably a progressive ulcer develops in the duodenum which causes death from hemorrhage or perforation. The occurrence of these ulcers may be prevented or at least delayed by the oral administration of calcium carbonate and powdered bone meal, but so far I have been unable to cure an ulcer already formed.

Permanent occlusion of the pancreatic ducts is best accomplished by doubly ligating and dividing the ducts, separating the pancreas completely from the duodenum and interposing the omentum between. Under such conditions the pancreas degenerates in a few months to a thin fibrous cord which on microscopic examination is found to consist of islets with small remnants of acinous tissue. No pancreatic juice whatever enters the duodenum; the animals lose weight, and the bulky stools associated with pancreatic insufficiency appear. Nevertheless, in a series of 17 animals operated on in this fashion in my laboratory ulcer developed in only 5—an incidence of 29 per cent. This incidence agrees fairly well with that reported by other investigators. Of course complete removal of the pancreas provides for the total absence of pancreatic juice in the duodenum, and it is in this case that the greatest discrepancy in the incidence of ulcer is found. During the past seven years over 300 pancreatectomized dogs have been studied in my laboratory for periods ranging from a few months to over two years. All these animals were carefully examined post mortem, and of this large number only 4 presented duodenal or gastric ulcer. These animals were fed the usual diet of bread, meat, milk and vitamin supplements but were not given alkalis in any form. Why does ulcer develop in the dog with a total pancreatic fistula in 100 per cent of the cases, while the animal whose pancreas has been removed remains almost immune? I cannot answer this question, and it suggests that the problem is not entirely one of failure of neutralization of the gastric acid by the sodium bicarbonate of the pancreatic juice.

Effect of Exclusion of Duodenal Juice from the Upper Intestine.—Exclusion of the duodenal juice may be accomplished by extirpation of the duodenum, an operation that was first demonstrated to be compatible with life by my associates and me in 1918.²⁶ In these experiments, although both bile and pancreatic juice also were excluded, ulcer was not observed. In 1922, Mann and Kawamura²⁷ reported the successful

26. Dragstedt, L. R.; Dragstedt, C. A.; McClintock, J. T., and Chase, C. S.: *Am. J. Physiol.* **46**:584, 1918.

27. Mann, F. C., and Kawamura, K.: *Ann. Surg.* **75**:208, 1922.

removal of the duodenum in experiments on dogs, cats and hogs; the jejunum was anastomosed to the pylorus, and the bile and the pancreatic ducts were implanted into the jejunum. In 2 of the 11 dogs on which this operation was performed, jejunal ulcer appeared and caused death by perforation. While this is the best experiment on the role of the duodenal juice, there remains even here the possibility that the implantation of the bile duct may have caused some obstruction and damage to the liver.

A consideration of the data, a portion of which has been summarized, indicates that it is perhaps safe to conclude that absence of pancreatic juice, bile and duodenal juice or possibly of any one of these secretions from the upper intestine may be expected to cause a progressive perforating ulcer in the duodenum. While the nature of the protective action of these secretions is not entirely settled, it is likely that protection is in part due to the neutralization of the hydrochloric acid of the gastric juice. In each case the effective substance is probably sodium bicarbonate, and its greater concentration in pancreatic juice probably makes this secretion the most important. There is no evidence, however, and little likelihood that absence of these secretions or reduction in their neutralizing properties is responsible for ulcer in man except in rare instances, as in the case reported by Morton.²⁸ The disease is one that commonly affects young and otherwise healthy adults without the usual symptoms and findings of biliary or pancreatic insufficiency.

The report of Anderson and Fogelson²⁹ that a relative decrease in the gastric mucin occurs in some patients with duodenal ulcer is interesting, and it is possible that a defect of this type in the neutralizing mechanism may be important. Further studies should be made.

EXCESSIVE CONTINUOUS SECRETION OF GASTRIC JUICE IN THE EMPTY STOMACH AS A CAUSE OF ULCER IN EXPERIMENTAL ANIMALS

As indicated in the preceding section, it seems unlikely that pancreatic juice, bile and succus entericus fail to reach the duodenum and that the absence of these secretions can account for any large number of ulcers in man. There remains, however, the possibility that an excessive volume of gastric juice might exhaust the neutralizing mechanism of the stomach and the duodenum and then attack the mucosa. An excessive secretion in the empty stomach should be especially dangerous since the buffering effect of the food is ordinarily so effective. Attempts have been made to provoke such a secretion in animals both by stimulating the secretory

28. Morton, C. B., and Graham, J. B.: *Ann. Surg.* **91**:73, 1930.

29. Anderson, R. K., and Fogelson, S. J.: *J. Clin. Investigation* **15**:169, 1936.

nerves in the vagi and by the use of histamine. In 1927, Silbermann³⁰ reported the occurrence of ulcer in the stomach and duodenum of dogs subjected to repeated sham feeding experiments. Double esophagostomy was performed on 23 dogs, and feeding was accomplished through the peripheral esophageal opening. These dogs were allowed to eat for forty to sixty minutes three times a day, the swallowed food escaping to the outside via the fistula. Ulcer developed in the stomach in every case in fourteen to forty-nine days. Similar sham feeding experiments were performed by Schmidt and Fogelson³¹ and in my laboratory; however, the results were negative; no ulcer appeared. Büchner, Siebert and Malloy³² reported the occurrence of ulcer in the stomach of rats after the repeated injection of histamine. Bürkle-de la Camp³³ found that the healing of acute ulcer produced by the injection of silver nitrate beneath the gastric mucosa of dogs was markedly delayed by the repeated injection of histamine, a finding subsequently confirmed by Flood and Howes.³⁴ The recent work of Walpole, Varco, Code and Wangenstein³⁵ is especially interesting and important. These workers secured continuous stimulation of the gastric glands by Code's method of implanting pellets of histamine mixed with beeswax into the muscles or beneath the skin. A copious continuous secretion of gastric juice resulted; this result could be obtained daily for long periods. Typical chronic perforating ulcer appeared in the stomach or the duodenum of all the common laboratory animals so treated.

EXCESSIVE CONTINUOUS SECRETION OF GASTRIC JUICE IN THE
EMPTY STOMACH AS A CAUSE OF ULCER IN MAN

The demonstration that excessive secretion of qualitatively normal gastric juice will produce ulcer in the stomach and duodenum of lower animals is obviously of the greatest significance from the standpoint of the clinical problem. No one can deny that the same effect would in all probability be produced in man were the experiment carried out. Further, there is plenty of evidence that an excessive volume of gastric juice is secreted by many, perhaps most, patients with ulcer, although the cause of the hypersecretion is unknown. The early gastroenterolo-

30. Silbermann, I. S.: *Zentralbl. f. Chir.* **54**:2385, 1927.

31. Schmidt, C. R., and Fogelson, S. J., cited by Fogelson, S. J.: *Internat. Abstr. Surg.* **65**:1, 1937; in *Surg., Gynec. & Obst.*, July 1937.

32. Büchner, F.; Siebert, P., and Malloy, P. J.: *Beitr. z. path. Anat. u. z. allg. Path.* **81**:391, 1928.

33. Bürkle-de la Camp, H.: *Deutsche Ztschr. f. Chir.* **220**:31, 1929.

34. Flood, C. A., and Howes, E. L.: *Surg., Gynec. & Obst.* **58**:136, 1934.

35. Walpole, S. H.; Varco, R. L.; Code, C. F., and Wangenstein, O. H.: *Proc. Soc. Exper. Biol. & Med.* **44**:619, 1940.

gists noted that the stomach contents of patients with ulcer after an Ewald test meal were more acid than those of normal people, and the concept of hyperacidity as a cause of ulcer arose. When Carlson pointed out that this acidity approached but did not exceed the acidity of pure normal gastric juice, the idea of a pathologic hyperacid gastric juice had to be abandoned in favor of the concept of hypersecretion of normal juice with deficient neutralization. On the basis of present information it seems likely that the patient with ulcer secretes more gastric juice in response to food taking than the normal person and also, what is perhaps more important, that he secretes more gastric juice when there is no obvious stimulant. This fact is illustrated in an observation I made several years ago and has been noted also by others. In several patients with duodenal ulcer, the stomach was lavaged in the evening to remove all traces of food, and constant aspiration was maintained all night to recover as much of the continuous secretion as possible. From 500 to 1,200 cc. of clear fluid was obtained with free acid that in 1 case reached 90 clinical units. Since this juice was obtained when the upper gastrointestinal tract was empty of food and the patient was asleep, it is clear that the usual stimuli (nervous and chemical) were not operating. Under similar conditions, normal persons yielded usually less than 300 cc. of secretion with free acid rarely above 50 clinical units and often entirely absent.

What is the cause of this excessive continuous secretion of gastric juice? Is it due to the continuous formation and absorption of gastrin or histamine into the blood stream or does it depend on abnormal activity of the nervous secretory mechanism? These questions remain unanswered, but there are various possibilities that may be explored.

The occurrence of acute ulcers in the duodenum and the stomach after extensive superficial burns (Curling's ulcer) is, according to Harkins,³⁶ more common than coincidence would allow. Can these ulcers in man be attributed to the absorption of histamine or similar products from the burned area in a manner analogous to that of the experimental histamine ulcers of Walpole, Varco, Code and Wangenstein? This possibility certainly must be considered, and studies should be made on the continuous secretion of gastric juice in patients with severe burns as well as on experimental animals. The allergic states represent another condition in which liberation of histamine in the body fluids occurs³⁷ and might therefore conceivably affect gastric secretion. Studies on the incidence of ulcer and on the continuous gastric secretion in such patients might yield interesting data.

36. Harkins, H. N.: *Surgery* **3**:608, 1938.

37. Dragstedt, C. A.: *Physiol. Rev.* **21**:563, 1941.

THE RELATION OF THE NERVOUS SYSTEM TO
GASTRODUODENAL ULCER

While the possibility of continuous absorption of gastric secretory stimuli, such as histamine, must be admitted as a cause for the hypersecretion in patients with ulcer, the view that the hypersecretion is due to abnormal activity of the vagus secretory mechanism seems more attractive at present. For a number of years many investigators have commented on the high incidence of ulcer in those persons whose occupations involve unusual anxiety, stress and strain and on the tendency for healed ulcers to recur during periods of great mental and emotional tension. Cushing³⁸ marshaled a good deal of evidence implicating disturbances in the central nervous system as a causative factor in ulcer and reported the occurrence of acute perforating ulcer in the stomach after operation for cerebellar tumor. Similar cases have been reported by Grant.³⁹ The central nervous system affects the gastrointestinal tract by causing variations in the tract's blood supply, motility and secretions. The concept that irritative lesions in the brain produce ulcer in the stomach through local vasoconstriction and anemia in the mucous membrane lacks experimental support. Attempts to produce ulcer by extensive ligation of gastric blood vessels have usually failed. Disturbances in motility, particularly pylorospasm, which may cause retention and prevent the regurgitation of the neutralizing juices of the duodenum into the stomach, seems to merit more consideration. However, on the basis of the available experimental evidence on the genesis of ulcers, a portion of which has been summarized in this paper, it seems most probable that the central nervous system plays an undoubted role in causing the disease through increasing the volume of gastric secretion. The patient with ulcer who secretes large amounts of gastric juice at night is commonly the young adult who presents the stigma of excessive nervous tension. The acute ulcers in the stomach and duodenum which have been reported following various intracranial operations might well be due to the secretion of acid gastric juice in the empty stomach brought on by stimulation of the gastric secretory centers as a result of the brain tumor itself or of operative trauma. Several years ago I had an opportunity to study the gastric contents of 3 patients during the first two or three days following their operations for brain tumor and to compare these findings with those obtained from patients after operations within the abdomen. In the cases of the latter, the contents secured by continuous aspiration were commonly mixed with duodenal secretions and were neutral or only slightly acid in reaction. In sharp contrast the patients who had had intracranial operations yielded from 400 to 1,100 cc.

38. Cushing, H.: *Surg., Gynec. & Obst.* **55**:1, 1932.39. Grant, F. C.: *Ann. Surg.* **101**:156, 1935.

per day of typical gastric juice with a high free acid content (80 to 110 clinical units). These findings require confirmation by a more extensive study, since, if true, they suggest that some type of medical management for ulcer should be instituted after operation on the central nervous system.

Section of the vagus nerves has been suggested and carried out a number of times for the treatment of duodenal ulcer. The literature in this field has been reviewed by Hartzell.⁴⁰ He found that in dogs the acidity of the gastric secretion in response to the ingestion of food was markedly reduced, particularly when the vagi were divided above the diaphragm. The effect of this operation on the continuous secretion seems not to have been investigated. Information of this kind, especially in cases of duodenal ulcer with marked hypersecretion, should be of the greatest importance.

SUMMARY

The chemical and mechanical traumas produced by the normal gastric content are not sufficient in themselves to cause ulcers in the normal gastric and duodenal mucosa and prevent them from healing or to delay materially the healing of extensive lesions artificially produced. This resistance to the digestive action of the normal gastric content is moreover not limited to the gastric and the duodenal mucosa but is displayed to a considerable extent also by such organs as the spleen, the kidney and the pancreas. Pure gastric juice, on the other hand, can destroy and digest all living tissues, including the wall of the stomach itself. In this effect the gross and the histologic appearance of the typical progressive ulcer and the associated gastritis in man are exactly reproduced in the experimental animal. Under normal conditions, the gastric wall is not digested away because it is not exposed to pure gastric juice. Food, which in the normal person is the stimulus for the formation of gastric juice, is also the chief factor which protects the tissues against its corrosive activity. Pancreatic juice, gastric and intestinal mucus, duodenal juice and bile (probably in the order named) constitute an additional mechanism which protects the duodenal and, to a certain extent, also the gastric and the jejunal mucosa. When excessive volumes of normal gastric juice are continuously secreted in experimental animals, this defensive neutralizing mechanism is overcome, and ulcer is produced. It is probable that in man a similar excessive secretion of gastric juice often occurs, and ulcer results. It seems likely that in most cases this hypersecretion is neurogenic and is abnormal in the sense that it operates when the stomach is empty and in the absence of the usual stimuli for gastric secretion.

40. Hartzell, J. B.: *Am. J. Physiol.* **91**:162, 1929.

PEPTIC ULCER AND GASTRIC SECRETION

WALTER LINCOLN PALMER, M.D., PH.D.

CHICAGO

The role of the digestive action of gastric juice in the problem of peptic ulcer has long been recognized by clinicians; this is evident from the use of such descriptive terms as "peptic," "erosive," "corrosive" and "digestive." The originator of this concept is not known, but possibly the thought came to Matthew Baillie, to John Abercrombie and to Cruveilhier also, for John Hunter had already (1778) raised the question of why the normal stomach does not digest itself. The theory was developed further during the nineteenth century, particularly during the latter half, and in 1910, Schwarz¹ enunciated his now famous and much disputed doctrine of "no acid—no ulcer." The purpose of the present paper is to discuss the present status of the subject and the therapeutic implications. Time and usage have apparently justified the selection of the term "peptic ulcer" to denote a specific lesion appearing in various definite locations along the digestive tube and possessed of a rather characteristic structure. The "peptic ulcers" of the esophagus, the stomach, the duodenum, the jejunum or the ileum do not essentially differ anatomically, or indeed functionally, from one another. Even the distinctions between acute, subacute and chronic lesions are not sharp. Konjetzny,² in his beautiful anatomic study, has clearly traced the transition from acute erosion to acute ulcer and thence to chronic ulcer. From a practical point of view, erosion and truly acute ulcer are of little importance for they heal quickly and usually produce few or no symptoms. The subacute and chronic lesions are more likely to produce clinical manifestations and hence are the ulcers to be primarily considered.

GASTRIC SECRETION IN RELATION TO PEPTIC ULCER

The most comprehensive statistical analysis of gastric secretion was that made by Vanzant and associates.³ These workers found that "there

From the Frank Billings Medical Clinic, Department of Medicine, the University of Chicago.

1. Schwarz, K.: Ueber penetrierende Magen- und Jejunalgeschwüre, *Beitr. z. klin. Chir.* **67**:96, 1910.

2. Konjetzny, G.: Die entzündliche Grundlage der typischen Geschwürsbildung im Magen und Duodenum, Berlin, Julius Springer, 1930, p. 80.

3. Vanzant, F. B.; Alvarez, W. C.; Eusterman, G. B.; Dunn, H. L., and Berkson, J.: The Normal Range of Gastric Acidity from Youth to Old Age: An Analysis of 3,746 Records, *Ann. Int. Med.* **49**:345, 1932.

was an increase of approximately 12 units of free acidity in the case of duodenal ulcer . . . In the case of gastric ulcer the mean free acidity was lower than normal by about 6 units . . . The incidence of achlorhydria was half of that observed in normal persons." (The test meal consisted of eight arrowroot cookies and 400 cc. of water.) In terms of response to any standard test meal, it has become clear that the gastric acidity in patients with peptic ulcer falls within the normal range, in that presumably normal persons with gastroscopically normal gastric mucosas may exhibit variations from no free acidity to values of 140 to 160 clinical units. In this sense, it is incorrect to speak of hypoacidity and hyperacidity or of hyposecretion and hypersecretion; almost anything is normal.⁴ Peptic ulcer occurs in persons with a low secretory rate as well as in those with a high secretory rate. Chronic peptic ulcer does not occur, however, in patients with complete and persistent achlorhydria—a subject to be discussed in detail later. In terms of response to a standard test meal, the secretory capacity of the stomach seems to be the same during the periods of quiescence and healing as it is during periods of activity.⁵ The secretory response to a test meal, even one containing histamine, probably does not measure or give a good indication of the total twenty-four hour secretion or, what is perhaps even more important, of the nocturnal so-called fasting or basal secretion. Clinicians have long been aware of the fact that the excessive continued night secretion constitutes one of the greatest difficulties in therapy. Sippy,⁶ Henning and Norpoth,⁷ Winkelstein,⁸ Palmer,⁹ Val Dez¹⁰ and others have shown that, as a rule, patients with ulcer do have a nocturnal secretion which exceeds in amount and acidity that observed in normal persons under similar

4. Carlson, A. J.: The Secretion of Gastric Juice in Health and Disease, *Physiol. Rev.* **3**:1, 1923. Heintz, E. L., and Welker, W. H.: Acidity Curves in Gastric, Duodenal and Mixed Ulcers, *Ann. Int. Med.* **3**:371, 1924.

5. Brown, C. F. G., and Dolkart, R. E.: Gastric Acidity During Recurrences and Remissions of Duodenal Ulcer, *Arch. Int. Med.* **60**:680 (Oct.) 1937.

6. Sippy, B. W.: Gastric and Duodenal Ulcer, *J. A. M. A.* **64**:1625 (May 15) 1915; Ulcer of the Stomach and Duodenum, in Christian, H. A., and Mackenzie, J.: *Oxford Medicine*, New York, Oxford University Press, 1921, vol. 3, p. 153.

7. Henning, N., and Norpoth, L.: Untersuchungen über die sekretorische Funktion des Magens während des nächtlichen Schlafes, *Arch. f. Verdauungskr.* **53**:64, 1933.

8. Winkelstein, A.: One Hundred Sixty-Nine Studies in Gastric Secretion During the Night, *Am. J. Digest. Dis.* **1**:778, 1935.

9. Palmer, W. L.: Fundamental Difficulties in the Treatment of Peptic Ulcer, *J. A. M. A.* **101**:1604 (Nov.) 1933.

10. Val Dez, F. C.: The Night Secretion of Free Hydrochloric Acid in the Stomach, *Illinois M. J.* **81**:149, 1942.

conditions. Wolfson and Wanowskaja¹¹ found that the hourly secretion of patients with ulcer was definitely and distinctly higher than that observed in normal persons. Bloomfield¹² observed that in terms of response to the histamine test the gastric secretion in patients with ulcer does not differ from that of normal persons but that there is a tendency toward a higher basal secretion. "Certain people, usually with duodenal ulcer, secrete under basal conditions a larger volume of gastric juice of higher acidity than is ever attained in normal asymptomatic individuals." There is thus abundant evidence that as a rule the gastric secretion in patients with peptic ulcer exceeds in amount secreted per hour and per twenty-four hours that found in normal persons.

PATHOGENESIS OF PEPTIC ULCER

In the studies of the pathologic anatomy of peptic ulcer mentioned before, Konjetzny presented satisfactory evidence that the lesion begins in the mucosa, that it increases in size and in depth by invasion and that it is definitely a penetrative process. Experimentally, Mann¹³ and numerous other workers¹⁴ have shown conclusively that the ulcer produced by them in diverse ways is also a penetrative invasive process identical in pathologic appearance, and indeed, in behavior, with peptic ulcer as seen in human beings.

The presence of acid gastric juice is essential for the production of such lesions. Indeed, it seems to be the one indispensable factor. "It should again be emphasized that chronic peptic ulcer has only been produced consistently experimentally by methods which prevent the neutralization, dilution or buffering of the gastric content as it passes from the stomach."¹³ This statement was made prior to the production

11. Wolfson, A. S., and Wanowskaja, R. L.: Untersuchungen der Magen-funktionen bei Ulkuskranken, *Arch. f. Verdauungskr.* **61**:191, 1937.

12. Bloomfield, A. L.: The Problem of Gastric Hyperacidity, *Am. J. Digest. Dis.* **6**:700, 1939.

13. Mann, F. C., in Eusterman, G. A., and Balfour, G. C.: The Stomach and Duodenum, Philadelphia, W. B. Saunders Company, 1936, p. 57.

14. (a) Code, C. F., and Varco, R. L.: Chronic Histamine Action, *Proc. Soc. Exper. Biol. & Med.* **44**:475, 1940. Hay, L.; Lynn, D., and Wangenstein, O. H.: The Production of Gastric and Duodenal Ulcer in Various Animals by the Intramuscular Implantation of Histamine in Beeswax, *Tr. Am. Soc. Exper. Path.*, 1941, p. 12. Varco, R. L.; Code, C. F.; Walpole, S. H., and Wangenstein, O. H.: Duodenal Ulcer Formation in the Dog by Intramuscular Injections of a Histamine Beeswax Mixture, *Am. J. Physiol.* **133**:P475, 1941. Walpole, S. H.; Varco, R. L.; Code, C. F., and Wangenstein, O. H.: Production of Gastric and Duodenal Ulcers in the Cat by the Intramuscular Implantation of Histamine, *Proc. Soc. Exper. Biol. & Med.* **44**:619, 1940. (b) Matthews, W. B., and Dragstedt, L. R.: The Etiology of Gastric and Duodenal Ulcer, *Surg., Gynec. & Obst.* **55**:265, 1932.

by Code, Varco, Wangensteen and co-workers^{14a} of typical chronic peptic ulcer in the dog and other animals as a result of continued hypersecretion induced by the injection of a slowly absorbable mixture of histamine and beeswax. Mann, however, had produced experimental ulcer by means of a continuous drip of hydrochloric acid into the stomach. Büchner and associates¹⁵ produced acute lesions in the stomach of the rat by the subcutaneous injection of histamine and confirmed the observations of Silbermann¹⁶ on the production of acute lesions in the dog by sham feeding. The paramount importance of acid in the production of experimental peptic ulcer thus seems inescapable. Pepsin greatly facilitates the process, but it alone will not destroy the mucosa. The chief protection against the acid attack on the cells of the mucosa seems to be provided by the thin layer of mucus with which they are covered. If this is wiped or rubbed away or dissolved, the cells are bathed in a medium containing a destructively high hydrogen ion concentration, together with the proteolytic enzyme, pepsin. Under such circumstances, ulcer develops. Factors such as thrombosis, embolism and infection are not essential features of experimental ulcer.

There is abundant clinical evidence that with ulcer in human beings the problem is also one of tissue resistance versus acid attack. It is well established that peptic ulcer occurs only in those portions of the digestive tract exposed to the action of acid gastric juice, i. e., the lower esophagus, the stomach, the first and second portions of the duodenum and, after gastroenterostomy, in the portions of the bowel adjacent to gastroenterostomy openings. Primary ulcer of Meckel's diverticulum and solitary peptic ulcer of the small bowel have been shown to occur adjacent to aberrant acid-secreting gastric mucosa.¹⁷ The constancy of this anatomic relation between peptic ulcer and gastric glandular tissue seems to be a thoroughly established pathologic fact.

The second important clinical observation is the occurrence of chronic peptic ulcer in only those persons whose gastric mucosa is able to secrete acid gastric juice. The erroneous concept that chronic peptic ulcer may occur with complete achlorhydria is based largely on informa-

15. Büchner, F.; Siebert, F., and Molloy, P. J.: Ueber experimentelle erzeugte akute peptische Geschwüre des Rattenvormagens, *Beitr. z. path. Anat. u. z. allg. Path.* **81**:391, 1928. Büchner, F.: Die Pathogenese der peptischen Veränderungen, Jena, Gustav Fischer, 1931.

16. Silbermann, I. S.: Experimentelle Magen-Duodenalulcuserzeugung durch Scheinfüttern nach Pavlow, *Zentralbl. f. Chir.* **54**:2385, 1927.

17. Brown, P. W., and Pemberton, J. de J.: Solitary Ulcer of Ileum and Ulcer of Meckel's Diverticulum, *Ann. Int. Med.* **9**:1684, 1936. Fleet, G. A.: Misplaced Gastric Mucosa as a Cause of Massive Rectal Hemorrhage, *Canad. M. A. J.* **42**:216, 1940. Johnston, L. B., and Renner, G.: Peptic Ulcer of Meckel's Diverticulum, *Surg., Gynec. & Obst.* **59**:198, 1934. Taylor, A. L.: Epithelial Heterotopias of Alimentary Tract, *J. Path. & Bact.* **30**:415, 1927.

tion gained from the old Ewald test meal or the fractional meal. The inadequacy of such criteria was shown in 1926.¹⁸ At that time, in a study of the records of 1,004 cases of proved peptic ulcer, satisfactory proof of achlorhydria was found in only 1 case, and in this instance at autopsy the ulcer was found to be healed. Since then, in approximately 2,500 cases of peptic ulcer, I have failed to find a single case of active chronic peptic ulcer with complete and permanent anacidity. Occasionally one sees a patient with a definite bilateral deformity of the duodenal bulb, a typical ulcer deformity, without roentgen evidence of an active ulcer crater, without ulcer symptoms and with histamine-achlorhydria. One such patient seen by me in 1933 gave a history of distress suggestive of ulcer dating from 1923 to 1925 or 1926. In the subsequent seven or eight years there had been apparently no distress of this sort. There are rare cases of pernicious anemia in which an ulcer deformity of the duodenal bulb is found by roentgen examination, but in no such instance coming to my attention has there been evidence, clinical or roentgenologic, of active ulcer. In 1940, Nutter and I¹⁹ analyzed the alleged cases of chronic ulcer with achlorhydria reported by others and found that none of them fulfilled the requirements stipulated in 1926. In a series of 84 cases of chronic gastric ulcer studied by us, there was no instance of achlorhydria. One patient, however, was of great interest because the maximum free acidity (histamine) was only 18 clinical units. Two cases were of considerable interest because of marked fluctuations in gastric secretion, the maximum free acidity (histamine) ranging from 0 to 75 and 79 degrees.

The importance of carrying out repeated histamine tests with careful technic in cases of achlorhydria, including the use of fluoroscopy to check the position of the tip of the tube in the stomach, is illustrated by a case in which four consecutive histamine tests of gastric secretion on June 15, 18, 24 and 25 all failed to disclose free acidity, and yet on June 30, abundant secretion was found, the free acidity reaching a peak of 76 units.¹⁹

Recently there has come to my attention, through the courtesy of Dr. Sidney Portis, detailed information of another apparent case of gastric ulcer with achlorhydria.

The patient, a man 64 years of age whose symptoms were epigastric distress of two months' duration with a loss of weight of 16 pounds (7.3 Kg.), was referred by Dr. Portis to Dr. Rudolf Schindler for gastroscopic examination on Aug. 17, 1939. Dr. Portis reported that the roentgen examination had disclosed a small lesion of the lesser curvature and the posterior wall of the stomach. An Ewald test meal on August 9 had disclosed no free acid and a total acidity of 18.

18. Palmer, W. L.: Mechanism of Pain in Gastric and Duodenal Ulcer: I. Achlorhydria, *Arch. Int. Med.* **38**:603 (Nov.) 1926.

19. Palmer, W. L., and Nutter, P. B.: Peptic Ulcer and Achlorhydria: A Further Study of the Role of Acid Gastric Juice in the Pathogenesis of Peptic Ulcer, *Arch. Int. Med.* **65**:499 (March) 1940.

On August 10, using a fractional Ewald test meal followed with histamine, Dr. Portis found the values listed in table 1. The gastroscopic examination disclosed a "large ulcer of the upper portion of the posterior wall, most likely carcinoma, type 3." The patient underwent operation at the Mayo Clinic on September 6; "a sub-acute hemorrhagic inflammatory ulcer" was found. No evidence of malignant change was noted in the sections.

This would appear to be satisfactory evidence of peptic ulcer with achlorhydria, yet the existence of persistent achlorhydria is not proved. The fallacy in this case is illustrated by the instance cited before in which four consecutive tests during an interval of ten days failed to disclose free acid, and yet abundant acid secretion was found a few days later.

Chronic peptic ulcer does occur, however, in patients with a low grade secretion. This is shown in table 2 in which are shown the results of protracted studies carried out on a patient under observation

TABLE 1.—*Free and Total Acidity in an Apparent Case of Gastric Ulcer with Achlorhydria After an Ewald Test Meal Followed with Histamine*

Time (A.M.)	Free Acidity	Total Acidity
9:50.....	0	15
10:05.....	0	16
10:20.....	0	16
10:35.....	0	20
10:50 (histamine injected).....	0	26
11:05.....	0	25
11:20.....	0	25

for almost six years. The patient, A. K., a woman, was born in 1873. The ulcer, when present, was invariably located on the lesser curvature of the stomach just above the angulus.

It is clear that in this case gastric ulcer recurred at intervals in a stomach with an extremely low secretory response to histamine. The question naturally arises as to whether the gastric juice in such a stomach interfered with the healing of the ulcer or played any role in causing recurrence. Obviously, hyperacidity was not present, and the secretion was considerably less than that ordinarily seen in normal persons. It may be that the resistance or the protection of the mucosal cells was unusually poor, with the result that even this gastric juice was sufficiently destructive to interfere with healing. On Dec. 6, 1939, when the maximum titratable free acidity in response to histamine was only 13 units, the p_H reading was 2.99. This is a hydrogen ion concentration adequate for the conversion of pepsinogen to pepsin. The optimum p_H for peptic activity, according to Hawk and Bergeim,²⁰ is between 2 and 3. "At about p_H 5 its power to digest protein disappears."

20. Hawk, P. B., and Bergeim, O.: *Practical Physiological Chemistry*, ed. 9, Philadelphia, P. Blakiston's Son & Co., 1927.

TABLE 2.—*Summary of a Study of a Patient with Gastric Ulcer*

Date	Fasting Secretion		Maximum Free Acidity (Histamine)	Roentgen Examination	Gastroscopic Examination
	Volume	Free Acidity			
1/2/36	Small gastric ulcer	
4/10	..	7 (Ewald)	..		
4/16	Shallow ulcer	
4/17	Healing benign ulcer
5/27	Ulcer almost healed	Ulcer almost healed
6/17	Healing ulcer
7/17	6	0	25	Chronic ulcer
7/18	Ulcer 3 mm in diameter	
10/23	Ulcer 1 cm. deep; 1 cm. wide	
10/28	Ulcer still present
12/10	Scar of healing ulcer
12/22	Ulcer 2 mm deep; 2 mm in diameter	
2/13/37	Ulcer healed	
3/17	Very small ulcer
3/25	No ulcer	
4/11	Small erosion at site of ulcer with scar formation
5/12	Shallow ulcer still present
5/15	No ulcer	
6/2	No ulcer	Chronic healing ulcer
7/	No active ulcer	
9/1	Chronic ulcer 1 cm. in diameter
12/2	Small shallow ulcer
1/5/38	Ulcer not healed
1/10	No active ulcer	
1/12	12	0	50	
2/9	Healed gastric ulcer
2/28	Ulcer healed
3/10	Scar only
3/15	No active ulcer	
3/29	Scar only
7/6	Recurrent ulcer 8 mm in diameter
7/7	25	0	4	
7/11	35	0	55	
7/12	Recurrent ulcer; 14 mm in diameter; 5 mm in depth	
7/15	20	0	12	
7/21	28	0	20	
7/28	12	0	29	
8/2	Ulcer healed	
8/4	10	0	25	
8/5	Recurrent ulcer
8/11	32	0	29	
8/18	22	0	45	
8/25	28	0	14	
8/26	Shallow ulcer
9/8	20	0	26	
9/23	30	0	28	
10/6	5	0	20	
10/20	44	0	30	
11/7	42	0	50	
11/10	Ulcer 9 mm in diameter	
11/19	Ulcer smaller
12/1	14	0	0	Ulcer present
12/2	
12/29	14	0	25	Ulcer almost healed
1/6/39	
1/20	22	0	66	Ulcer healed	
1/27	Ulcer healed
2/24	Two ulcers at old site
3/10	25	0	17	
3/24	No active ulcer	Large crater
3/27	Benign ulcer in old scar
3/30	10	0	30	
4/3	Slightly more shallow
4/17	Slightly smaller
5/20	35	0	34	
6/3	30	0	35	
6/23	3	Large ulcer still present
7/5	No active ulcer	
7/14	Ulcer about 15 mm in diameter
9/20	75	0	41	

TABLE 2.—Summary of a Study of a Patient with Gastric Ulcer—Continued

Date	Fasting Secretion		Maximum Free Acidity (Histamine)	Roentgen Examination	Gastroscopic Examination
	Volume	Free Acidity			
9/27	Small ulcer	
10/ 2	Large benign ulcer
10/19	0	0	34		
10/20	Ulcer present	
10/23	Huge benign ulcer about 15 mm. in diameter
11/ 3	Large healing ulcer
11/10	5	0	26		
11/13	Marked decrease in size of ulcer	
11/22	18	0	4		
11/24	Very shallow ulcer	
11/25	14	0	0		
11/26	12	0	0		
11/27	4	0	0		
11/29	0	0	0		
12/ 1	0	0	0	Ulcer healed
12/ 2	0	0	0		
12/ 5	Ulcer almost healed	
12/ 6	6	0	13	Ulcer scar with converging fold
12/ 7	8	0	0		
12/13	11	0	0		
12/15	49	0	0		
12/18	57	13	35		
12/20	40	0	18		
12/22	40	0	26		
12/28	22	0	0		
1/ 4/40	23	0	0		
1/11	8	0	0	Ulcer healed
1/25	26	0	10		
2/ 1	25	0	12		
2/ 8	15	0	4		
2/16	Ulcer on old scar
2/23	21	12	35		
3/ 1	Ulcer healing
3/ 7	31	0	32		
3/15	Ulcer rather deep
3/18	Recurrent ulcer	
3/20	58	0	24		
3/29	Ulcer still present
4/10	58	0	22		
4/12	Very shallow ulcer
4/26	56	0	24		
4/29	Ulcer healed	
5/ 3	38	10	45		
5/17	Benign ulcer
6/13	15	0	32		
6/21	Rather small ulcer
7/15	Ulcer not as deep
8/26	Ulcer about 15 mm. in diameter
8/27	25	0	20	Healed gastric ulcer	
10/ 7	No change
11/18	Ulcer smaller
12/ 2	30	0	36		
1/ 6/41	Ulcer healed or almost healed
1/20	26	11	31		
2/ 3	Ulcer still visible
2/24	No active ulcer	
3/10	Ulcer about 7 mm. in diameter
4/ 7	Ulcer 5 or 6 mm. in diameter
4/21	70	5	32		
4/28		
5/ 3	Scar but no active ulcer	
5/12	No change
5/26	30	0	27		
6/ 2	No change
6/30	Ulcer about 3 mm. in diameter
7/21	31	0	0		
8/25	Ulcer entirely healed
10/ 3	Recurrent shallow ulcer
10/17	Shallow ulcer 3 mm. in diameter
10/31	11	0	13		

The same remarks apply to an interesting case recently studied through the kindness of Dr. George F. Dick.

The patient, J. W., was a man aged 50 who entered Albert Merritt Billings Hospital with a history of intermittent epigastric distress of six years' duration. There was a definite history of syphilis, but repeated blood Wassermann and Kahn tests at the time of hospitalization were negative; the spinal fluid examination also gave negative results. Roentgen examination on Aug. 23, 1941, disclosed a probably benign penetrating ulcer of the lesser curvature (fig. 1). Gastroscopic examination by Dr. Schindler revealed an unusual ulcer of the lesser curvature of the stomach with no evidence of malignant change. The gastric analyses are given in table 3.

Subsequent roentgen examinations showed a marked decrease in the size of the ulcer and complete disappearance of the niche by September 25. The patient



Fig. 1.—Roentgenogram of penetrating ulcer of the lesser curvature of the stomach just below the cardia taken on Aug. 23, 1941.

died suddenly on October 2. Autopsy disclosed syphilitic aortitis with apparently complete occlusion of the left and marked narrowing of the right coronary ostium. The gastric ulcer was found to be completely healed (fig. 2). On histologic examination, no significant evidence of syphilis was found in the healed lesion, although the possibility could not be excluded completely.

Rodgers and Jones²¹ described a type of acute or subacute small gastric ulcer, 2 to 5 mm. in diameter, not detected by roentgen examination and found by gastroscopic examination only in the presence of a "thin, atrophic mucosa and associated with absence or diminution in the secretion of acid." The ulcers were not seen at subsequent

21. Rodgers, H. W., and Jones, F. A.: Subacute Ulceration of Stomach Associated with Atrophy of the Gastric Mucosa and with Absence or Diminution in Secretion of Hydrochloric Acid, *St. Barth. Hosp. Rec.* 71:140, 1938.

examinations two to four weeks later. Seventeen such cases were encountered in 600 gastroscopic examinations. One patient had pernicious anemia and a strongly positive Wassermann reaction. Seven of the 17 had histamine achlorhydria. Rodgers and Jones stated that they had never seen "large chronic gastric ulcers . . . in patients with a uniformly thin mucosa and either a low acid curve or achlorhydria." Schindler and I, in our combined studies, have not as yet seen such acute ulcer in patients with complete and persistent achlorhydria. In 4,277 examinations with the flexible gastroscope, Schindler²² conducted 69 gastroscopies in 48 patients with pernicious anemia without encountering a single instance of the type described by Rodgers and

TABLE 3.—*Gastric Analyses of a Patient with Ulcer of the Lesser Curvature of the Stomach*

Date.....	Histamine, Mg.	Highest Acidity	
		Clinical Units (Titrated)	pH (Beckman)
8/26/41.....	0.65	0	...
8/30	0.65	0	...
9/17	1.0*		
	0.5†	7	...
	0.5†	13	...
9/23	0.9	0	4.2
9/25	1.0	0	7.35
	0.5†	0	3.7
	0.5†	3	2.92
9/30	1.0	0	6.17
	0.5†	0	3.79
	0.5†	7	2.75

* The first histamine test on September 17 was excluded because fluoroscopic examination disclosed the tip of the tube to be in the duodenum at the ligament of Treitz. The figures given are for the second test performed when the tube was in the stomach. The position of the tube was not checked in the examinations of August 16 and 30. It was verified in the examination of September 23.

† Test made twenty minutes after the preceding test.

Jones. Gutzeit²³ reported finding, during one gastroscopic examination, acute ulcer in a patient with pernicious anemia and histamine-proved anacidity and without ulcer symptoms. The diagnosis was not confirmed by further gastroscopic or roentgen studies. The possibility exists that small acute ulcer may appear in the presence of persistent histamine achlorhydria. The occurrence cannot be considered, however, as completely proved. Large chronic ulcer apparently develops only in an acid-secreting stomach. The validity of this conclusion is further shown by the failure of Kahn²⁴ to find a single peptic ulcer in 840

22. Schindler, R.: Personal communication to the author.

23. Gutzeit, K.: *Die Gastroskopie im Rahmen der klinischen Magendiagnostik*, Berlin, Julius Springer, 1929.

24. Kahn, J. R.: Absence of Peptic Ulcer in Pernicious Anemia, *Am. J. M. Sc.* 194:463, 1937.

cases of pernicious anemia and by the failure of Washburn and Rozendaal²⁵ to find an ulcer in 906 consecutive cases of pernicious anemia.

The experimental ulcer of Code, Varco and Wangenstein^{14a} produced by prolonged gastric secretion resulting from the injection of histamine suspended in beeswax apparently has a clear clinical counterpart in the ulcer of Curling.²⁶ Necheles and Olson found experimentally that after extensive burns there is a "rapid and sustained increase in gastric secretion amounting to several hundred per cent."

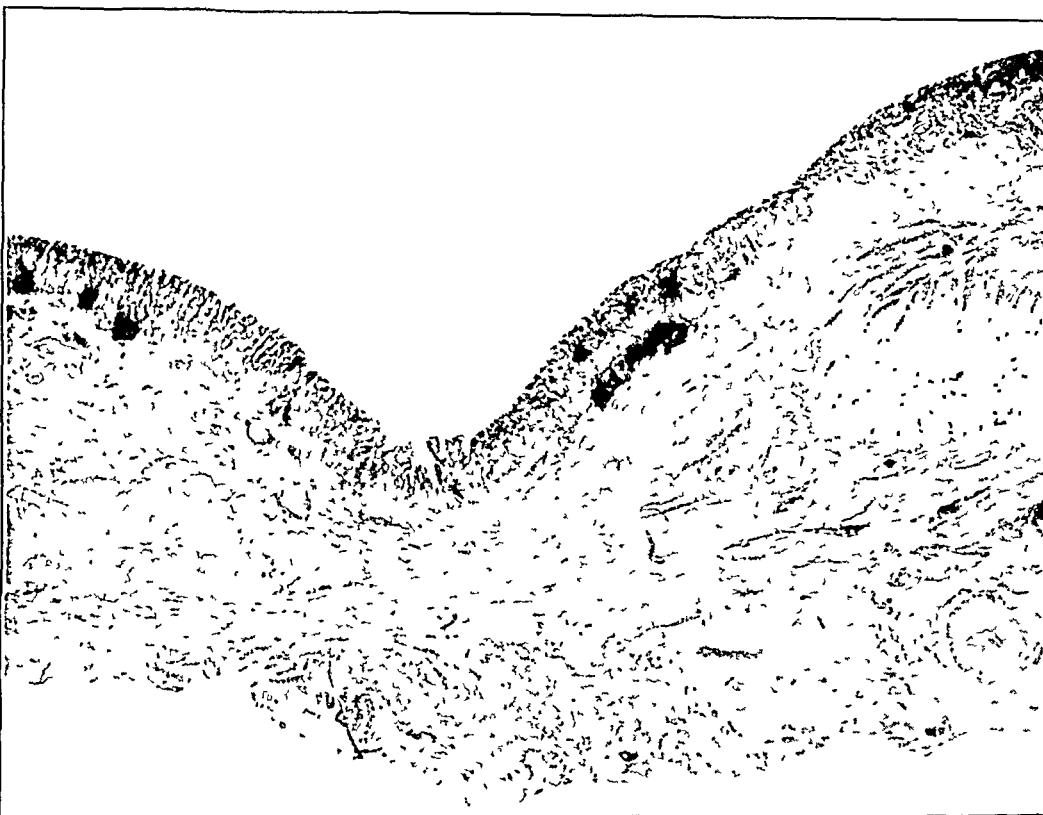


Fig. 2.—Photomicrograph ($\times 8$) of healed gastric ulcer. Note the complete regeneration of the mucosa with complex tubular glands and the fusion of the muscularis mucosae with the muscularis propria in the scar tissue of the healed ulcer.

Code and Macdonald²⁷ found a marked rise in the histamine-like activity of the blood following burns. Rosenthal²⁸ found this histamine-

25. Washburn, R. N., and Rozendaal, H. M.: Gastric Lesions Associated with Pernicious Anemia, *Ann. Int. Med.* **11**:2172, 1937.

26. Harkins, H. N.: Acute Ulcer of the Duodenum (Curling's Ulcer) as a Complication of Burns: Relation to Sepsis, *Surgery* **3**:608, 1938.

27. Code, C. F., and Macdonald, A. D.: The Histamine-Like Activity of Blood, *Lancet* **2**:730 1937.

28. Rosenthal, S. R.: The Toxin of Burns, *Ann. Surg.* **107**:111 and 257, 1937.

like substance to differ from histamine in various respects such as heat lability. The evidence strongly suggests, however, that Curling's ulcer is a result of excessive gastric secretion induced by the presence in the blood of histamine or a histamine-like toxin produced by the burn.

It seems clear, then, in summary, that peptic ulcer results from a failure of the cells of the mucosa and of the wall of the stomach or the intestine to withstand the digestive action of acid gastric juice. The cause of the failure is not clear. Perhaps the secretion of protective mucus is insufficient. Perhaps the cellular resistance or cellular viability, whatever these terms may mean, is inadequate. In any event, the acid attack exceeds the capacity of the protective mechanism. Absolute hyperacidity need not be present, but merely a relative hyperacidity, as Büchner pointed out. It is relative in the sense that the hydrogen ion concentration and the proteolytic activity of the gastric juice exceed in destructive effect the defensive capacity of the cell. Tissue necrosis and digestion thus take place and lead to an erosion. Healing may occur, or the process may continue to the formation of acute ulcer. At any stage the lesion may heal, simply persist (becoming either subacute or chronic) or it may increase in size.²⁹ Regenerative activity is present at all times; whenever it becomes dominant, healing occurs.

MECHANISM OF PAIN

A comprehensive consideration of the mechanism of gastric pain, and specifically of the pain of peptic ulcer, is beyond the scope of this paper. Continued experience, however, has been in accord with the view expressed in 1926,³⁰ that acid gastric juice is primarily responsible not only for the development and the extension of the ulcer but also for the concomitant inflammation (a true chemical inflammation) and for the pain as well. Active inflamed ulcer, the inflammation resulting from the acid attack, is a sensitive lesion. The visceral nerves, ordinarily insensitive to such stimuli as cutting, pinching and tearing, become sensitive to both mechanical and chemical irritation. Carlson and other workers,³¹ using the balloon and kymograph method, showed that under such circumstances, the pain threshold is crossed by the mechanical stimuli arising from peristalsis. In 1 patient studied during

29. Palmer, W. L.; Schindler, R., and Templeton, F. E.: Development and Healing of Gastric Ulcer: A Clinical, Gastroscopic and Roentgenologic Study, *Am. J. Digest. Dis.* **5**:501, 1938.

30. (a) Palmer, W. L.: The Production of Pain by Means of Chemical Irritants, *Arch. Int. Med.* **38**:694 (Dec.) 1926; (b) The Pain of Gastric Carcinoma, *ibid.* **39**:126 (Jan.) 1927. (c) Palmer, W. L., and Heinz, T. E.: Further Observations on the Mechanism of Pain in Gastric and Duodenal Ulcer, *ibid.* **53**:269 (Feb.) 1934.

31. Palmer, W. L.: Role of Peristalsis and Spasm, *Arch. Int. Med.* **39**:109 (Jan.) 1927.

operation under local anesthesia, Dragstedt and Palmer³² found the ulcer exceedingly sensitive to the slight trauma of lightly stroking the serosal surface. Pinching and circular spasm of the muscle in the region of the ulcer evoked severe pain. The flow of acid on the surface of the ulcer likewise evoked pain. Palmer^{30a} had previously shown that the injection of acid gastric juice or of a solution of hydrochloric acid into the stomach is sufficient to evoke pain in a peptic ulcer, provided the pain mechanism is sensitive at the time of the injection. The manner in which the pain threshold may be traversed by the action of acid is illustrated in the following episode:

A man 49 years of age who had suffered with recurring duodenal ulcer for nearly twenty years was admitted to the hospital for treatment. His pain was severe. Roentgen examination disclosed a large crater in the duodenum. Toward the end of a histamine test revealing a free acidity ranging from 90 to 100 clinical units, such severe pain developed that the patient doubled up in bed. Four grams of sodium bicarbonate dissolved in 100 cc. of water were allowed to run into the stomach through the tube. Complete and spectacular relief occurred within two to three minutes, according to the intern's note. In time, after ulcer management, the pain-producing mechanism of the lesion became desensitized; this was evidenced by the fact that all spontaneous pain disappeared, and repeated histamine tests were carried out without pain. No other acid tests were made.

In another patient, a man 43 years of age, severe continuous pain radiating through to the back apparently required frequent injections of morphine for relief. With the demonstration of a duodenal crater and a histamine-free acidity of 108 clinical units, the patient was submitted to a program of acid neutralization with spectacular relief from the pain. Subsequently, an acid test was carried out; 200 cc. of a 0.5 per cent solution of hydrochloric acid was injected into the empty stomach. Typical pain developed in the back and progressively increased in severity during the course of twenty minutes. The pain was said by the patient to have been exactly like that experienced in his previous most severe attacks. The injection of 4.0 Gm. of sodium bicarbonate in 60 cc. of water was followed by gradual subsidence of the pain; complete relief was obtained in twenty to thirty minutes. With continued antacid ulcer management the spontaneous pain ceased entirely; the ulcer crater disappeared in the roentgenograms, and at the end of six weeks, the patient was able to tolerate three separate injections at thirty minute intervals of 200 cc. each of 0.5 per cent solution of hydrochloric acid with no distress whatsoever during the ninety minutes of the test.

As noted previously, this desensitization of the pain mechanism followed treatment designed to protect the ulcer from the corrosive action of the gastric juice and coincided with roentgen evidence of progressive healing. The dominant role of acid gastric juice in the entire process thus seems apparent.

With regard to the precise mechanism of the production of pain, it seems clear that the first essential is a lowering of the pain threshold of the nerve endings, presumably as a result of inflammation. The pain derived from mechanical irritation is apparently a pressure phenomenon.

32. Dragstedt, L. R., and Palmer, W. L.: Direct Observation on the Mechanism of Pain in Duodenal Ulcer, *Proc. Soc. Exper. Biol. & Méd.* **29**:753, 1932.

The pain induced by the acid is, in all probability, due to the direct irritation of the nerve endings by the acid solution. Moore and associates³³ found that solutions as weakly acid as p_H 6.0 produced stimulation of the nerve endings in blood vessels and capillary loops. Solutions as slightly alkaline as p_H 9.2 produced similar effects. In a peptic ulcer, nerve endings are exposed to solutions whose p_H is between 1 and 2 for several hours of every day. The puzzle, it would seem, is not the appearance of pain, but rather the absence of pain in certain cases. These may be rather insensitive persons with high pain thresholds in whom the digestive action of the gastric juice succeeds in destroying tissue but does not succeed in producing sufficient inflammation to lower the pain threshold to the point necessary for the production of pain.

THE HEALING OF PEPTIC ULCER

All ulcers may and the majority do heal in spite of the presence of acid gastric juice. This is evidenced by the spontaneous remissions so characteristic of the disease and by the healed lesions encountered in routine autopsy work. In all ulcers, regenerative processes begin early and continue until the tissue is destroyed or healing occurs. Apparently the balance of these tissue-regenerating and tissue-digesting processes is a delicate one, easily tipped one way or the other, and leading either to healing or to extension of the ulcer. Whether or not the remissions, the healing and the recurrences are related, wholly or partially, to variations in gastric secretion is not known. From the evidence offered of the role of acid digestion in the pathogenesis of ulcer, one would expect a priori that healing would occur more rapidly and more surely when the lesion is protected from the action of acid gastric juice. Daily clinical experience supports this concept. Some years ago an attempt was made to obtain more definite objective evidence on this point by subjecting two comparable groups of hospitalized patients to programs of therapy which differed only in that alkali was administered to one group in large amounts, while beef extract was given the other group as a substitute for the alkali. The design was to neutralize the gastric acidity in the group given alkali and to stimulate acid secretion in the group given beef tea.³⁴ The diet was the same for both groups. The rates of disappearance of spontaneous pain and of desensitization to the acid test were used as criteria of rates of healing, since subsidence of the inflammatory reaction is presumably the first step in the healing process. The average duration of spontaneous pain was two and eight-tenths days for those given alkali and

33. Moore, R. M.; Moore, R. E., and Singleton, A. O.: Experiments on the Chemical Stimulation of Pain-Endings Associated with Small Blood Vessels, *Am. J. Physiol.* **107**:594, 1934.

34. Palmer, W. L.: The Value of Acid Neutralization in the Treatment of Gastric and Duodenal Ulcers, *Arch. Int. Med.* **46**:165 (Aug.) 1930.

twenty-six and six-tenths days for those given beef tea. The average duration of sensitivity to the acid test was nine and seven-tenths days for those given alkali and twenty-six and nine-tenths days for those given beef tea. It thus seems clear that the neutralization of the acid facilitated the process of healing.

There is a great deal of direct and indirect evidence that the problem of ulcer therapy would be solved if there were available a safe and suitable method of producing complete and permanent achlorhydria. There is none, that is, none short of total gastrectomy. Conversely, the continued secretion of abundant highly acid gastric juice constitutes the greatest hindrance to healing. Such secretion not infrequently occurs with or without stenosis and obstruction, either spastic or cicatricial. Gastric ulcer is frequently accompanied by pylorospasm, benign hypertrophy of the pylorus, antral spasm or, indeed, by active or healed intrapyloric ulcer with resultant delay in gastric emptying and prolongation of the period in which the ulcer-bearing surfaces of the stomach and the duodenum are bathed in acid gastric juice. The case summarized in considerable detail on page 9, however, constitutes an exception in that gastric secretion was low and no evidence of a delay in gastric emptying was observed at any time. It is tempting to ascribe the poor healing and frequent recurrences seen in this instance to a poor *vis conservatrix* or *formativa*, for the patient seemed to have little *vis vitalis*! The fact that marked differences do occur in the healing capacities of the tissues in different persons is well known, but the underlying causes are obscure.

METHODS OF PROMOTING HEALING OF PEPTIC ULCER

The most effective means of promoting healing is to prevent the ulcer from coming into contact with acid gastric juice. Duodenal ulcer treated by Finsterer's *resectio ad exclusionem* invariably heals. Duodenal ulcer heals regularly after gastroenterostomy, presumably because this procedure provides sufficient diversion of the pyloric stream. Gastroduodenostomy likewise is followed by disappearance of the initial lesion. Pyloroplasty, as might be expected, does not give such uniform results. The chief difficulty with these various surgical therapeutic procedures, including subtotal gastrectomy, is not that they fail to lead to the healing of the primary ulcer but rather that new ulcers form at the new stomas.

Medical methods for promoting the healing of a given lesion are less certain and less spectacular. The oldest procedures (so old that their origin is shrouded in the clouds of antiquity) are rest and a milk diet. Little is known about the effects of exercise and rest on the digestive process, but there is some evidence that exercise increases gastric secretion. The effect of worry and nervous strain on secretion and on gastric emptying likewise needs further elucidation. With regard

to the milk diet, however, definite information is available, for milk is one of the best neutralizers of acid gastric juice; for example, 10 cc. can neutralize 11 cc. of 0.3 per cent hydrochloric acid.³⁵ All protein foods have definite neutralizing value. This capacity is utilized consciously or unconsciously in the various frequent feeding programs. The origin of the use of alkali in the treatment of peptic ulcer, like that of rest and a milk diet, is so old that its source is unknown. Sippy was the first to develop a comprehensive program of acid neutralization based on the use of food and alkali. A complete discussion of the details of management is beyond the scope of this paper.³⁶

The inhibition of gastric secretion is difficult to accomplish. Atropine does diminish the volume and, if given in therapeutically impossible dosage, ultimately the free acidity also.³⁷ It inhibits gastric emptying. Figure 3, provided by my associate, Dr. Alfred J. Klein, illustrates the manner in which 1.0 mg. of atropine injected subcutaneously prior to feeding inhibits the immediate postfeeding secretion of a modified Heidenhain pouch in the dog. The prolongation of the period of secretion is noteworthy. Presumably this is due to two factors: (1) escape from the effect of atropine and (2) delayed gastric emptying with a rise in pouch secretion as the stomach resumes emptying. Atropine given after the meal is rather less effective, but the same general action may be seen. The effect observed is primarily on the volume of the secretion rather than the acidity, as other workers have noted, for the acidity of the pouch secretion ranges from 120 to 160 unless the volume becomes markedly depressed; when this happens, the acidity also drops.

Various extracts capable of depressing gastric secretion and resembling enterogastrone³⁸ have been obtained from urine, but none

35. Freezer, C. R. E.; Gibson, C. S., and Matthews, E.: A Contribution to the Study of Alkalis as Therapeutic Agents, *Guy's Hosp. Rep.* **78**:191, 1928.

36. Kirsner, J. B., and Palmer, W. L.: The Effect of Various Antacids on the Hydrogen-Ion Concentration of the Gastric Contents, *Am. J. Digest. Dis.* **7**:85, 1940. Palmer, W. L.: Diseases of the Stomach, in Barr, D. P.: *Modern Medical Therapy in General Practice*, Baltimore, Williams & Wilkins Company, 1940, vol. 2, pp. 2261-2286; Peptic Ulcer, in Portis, S. A.: *Diseases of the Digestive System*, Philadelphia, Lea & Febiger, 1941, pp. 513-533; Diseases of the Stomach, in Cecil, R. L.: *A Textbook of Medicine*, ed. 5, Philadelphia, W. B. Saunders Company, 1940, pp. 776-792. Freezer, Gibson and Matthews.³⁵

37. Porter, R. T.: Studies on the Effect of Atropine on Gastric Secretion, *Proc. Soc. Exper. Biol. & Med.* **29**:504, 1932.

38. Culmer, C.; Atkinson, A. J., and Ivy, A. C.: Depression of Gastric Secretion by the Anterior Pituitary-Like Fraction of Pregnancy Urine, *Endocrinology* **24**:631, 1939. Gray, J. S.: Present Status of Urogastrone, *Am. J. Digest. Dis.* **8**:365, 1941. Friedman, M. H. F., and Sandweiss, D. J.: The Gastric Secretory Depressant in Urine, *ibid.* **8**:366, 1941. Gray, J. S.; Bradley, W. B., and Ivy, A. C.: On Preparation and Biological Assay of Enterogastrone, *Am. J. Physiol.* **118**:463, 1937. Quigley, J. P.: Enterogastrone: Significant Steps in the Development of Present Conceptions, *Am. J. Digest. Dis.* **8**:363, 1941.

of these substances has as yet been widely available for clinical study. Metz and Lackey³⁹ were led to use posterior pituitary in the treatment of peptic ulcer by noting polyuria associated with the ulcer syndrome. The patients received 40 mg. four times daily by nasal insufflation. "The excellent results obtained in this series were striking." I have had no clinical experience with this method, but Dr. Klein has made some interesting experimental observations. Figure 4 shows the marked

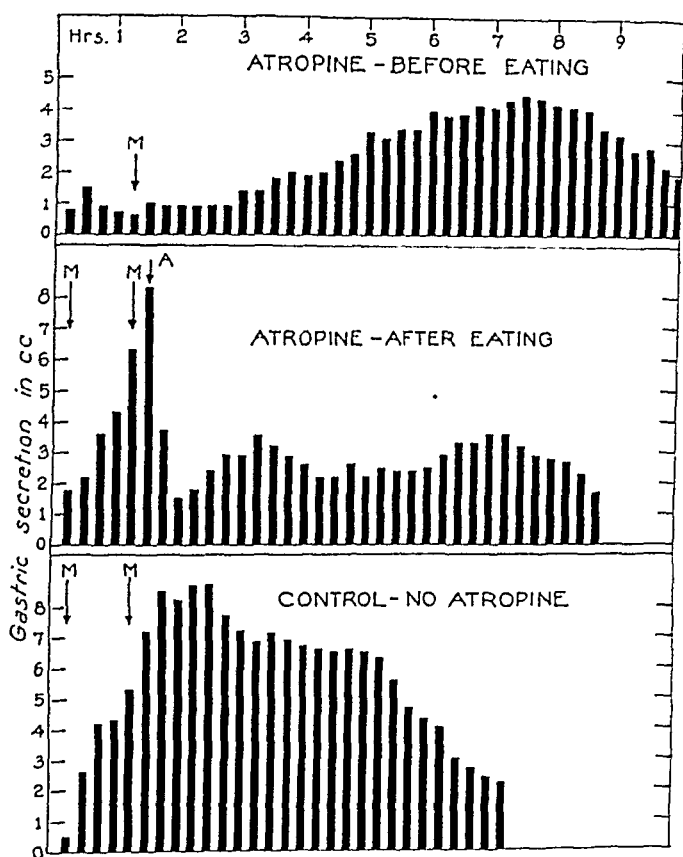


Fig. 3.—The effect of atropine on the volume of gastric secretion of a dog with a Heidenhain pouch. The bars represent cubic centimeters of secretion in fifteen minute periods. *M* indicates the feeding of a 100 Gm. bolus of meat. In the top section (average of six experiments in 3 dogs) 1 mg. of atropine was injected subcutaneously before the feeding; in the middle section (average of seven experiments in 3 dogs) the atropine was injected following a double meal; the control studies (average of seven experiments in 4 dogs) are shown in the bottom section.

and prolonged inhibition of gastric secretion in a dog with a modified Heidenhain pouch induced by the intramuscular injection of 2 cc. of

39. Metz, M. H., and Lackey, R. W.: Peptic Ulcer Treated by Posterior Pituitary Extract, *Texas State J. Med.* 34:214, 1938.

solution of posterior pituitary. In figure 5 a similar although less spectacular effect may be noted from the intranasal insufflation of posterior pituitary in the form of powder. Klein and Schindler observed gastroscopically that the gastric mucosa of the dog during the period of this effect changes from orange red to snow white, indicating presumably intense vasoconstriction.

Intensive radiation therapy results in a variable depression of gastric secretion lasting a variable time. In 88 patients treated by Palmer and

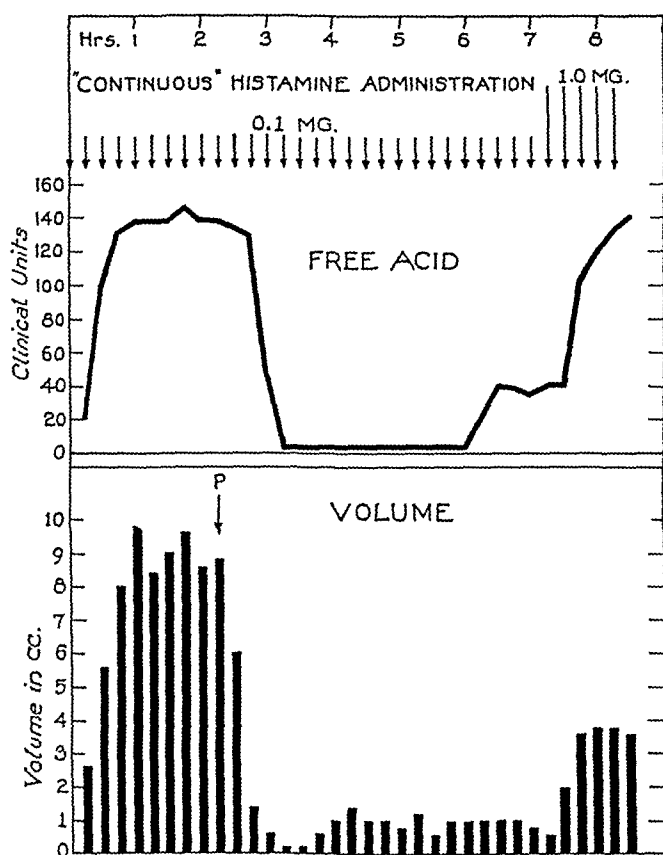


Fig. 4.—The effect of surgical pituitrin on the gastric secretion of a dog with a Heidenhain pouch. The profuse highly acid secretion induced by the subcutaneous injection at fifteen minute intervals of 0.1 mg. of histamine biphosphate is abruptly inhibited by the subcutaneous injection of 2 cc. of surgical pituitrin at P.

Templeton,⁴⁰ complete histamine achlorhydria developed in 35 and persisted for periods of a few days to a few months. During the phase of achlorhydria symptoms of ulcer were invariably absent, and healing progressed. Failure of the ulcer to heal and recurrence of the ulcer occurred only in those cases in which achlorhydria did not develop or after the phase of achlorhydria had passed.

40. Palmer, W. L., and Templeton, F. E.: The Effect of Radiation Therapy on Gastric Secretion, *J. A. M. A.* **112**:1429 (April 15) 1939.

Figure 6 illustrates the various effects noted.

One patient received 3,600 r, and yet the depression as measured by the maximum free acidity following histamine was relatively slight and transitory. This patient, a man of 56, entered the hospital with an ulcer of only three years' duration but with roentgen evidence of a duodenal ulcer with an enormous crater and with moderate stenosis. At the time of writing, the patient has followed an antacid ulcer regimen meticulously for the past three and a half years. The crater disappeared within a few weeks and has not recurred, nor has the stenosis increased. There has been no return of symptoms. Of the rather large group

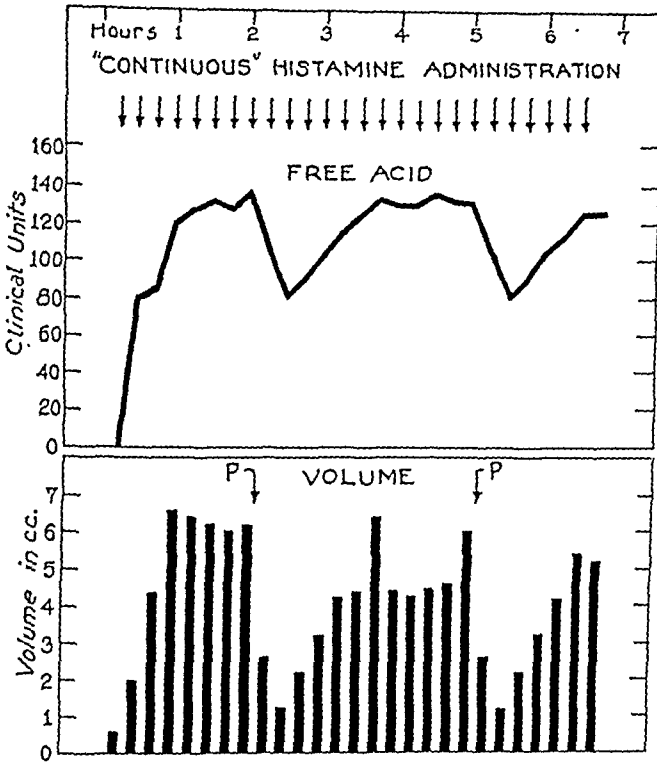


Fig. 5.—The effect on gastric secretion of the intranasal insufflation of posterior pituitary powder. The abundant continuous secretion of a dog with a Heidenhain pouch resulting from the subcutaneous injection of 0.1 mg. of histamine biphosphate every fifteen minutes is definitely, although incompletely, inhibited by the intranasal insufflation of 40 mg. of posterior pituitary powder (U. S. P. XI).

subjected to roentgen therapy, this patient was one of those whose gastric secretion was least affected.

A more typical response is that exhibited by the first patient treated by Templeton and me. The patient, a man 35 years of age, was seen in 1930 with stenosing duodenal ulcer of indefinite duration. Gastroenterostomy was performed in 1933 and undone in 1936 because of recurrent jejunal ulcer. The duodenal ulcer recurred, and in April 1937, the patient was given 2,930 r of therapy; after this complete achlorhydria to histamine developed and persisted from the twenty-seventh to the hundred and thirteenth day, returning to approximately normal by the two hundred and thirty-seventh day. The patient was advised to resume

his antacid program with the return of normal acidity but did so only to a limited extent. Moderate symptoms have recurred occasionally, and at times there has been roentgen evidence of a small crater in the duodenum, although the differentiation in this case between scar and crater has proved difficult.

In another case occurred the most prolonged depression observed. The patient, a man 38 years of age, entered the hospital with a history of ulcer of eight years' duration and a crater on the lesser curvature of the stomach about 1 cm. in diameter as seen roentgenologically. With medical management the symptoms were promptly relieved, and the crater disappeared. Roentgen therapy (2,937 r given in June 1937) resulted in complete achlorhydria to histamine appearing on the ninety-sixth day. As may be seen from figure 6, this persisted until the four

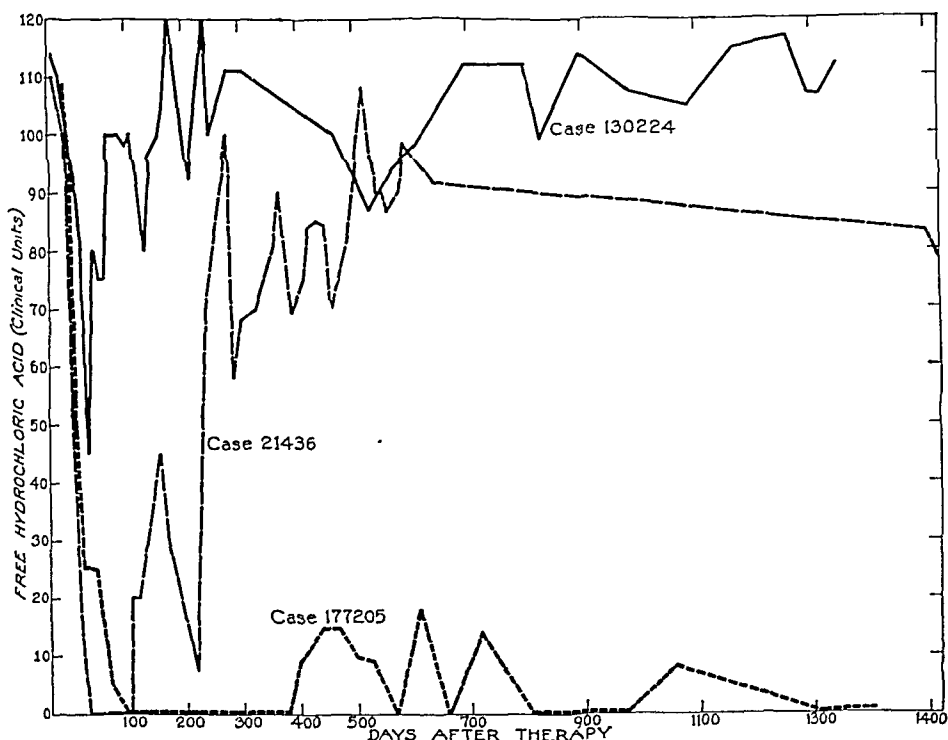


Fig. 6.—The depression of gastric acidity by roentgen therapy. Three cases illustrating the varying results obtained. The curves are based on the maximum free acidity present in individual histamine tests (see text).

hundred and fourth day. The gastric secretion at the end of four years was still extremely low. There have been no digestive symptoms of any kind. Roentgen and gastric studies have disclosed no evidence of ulcer. For the past three years the patient has eaten a general diet.

INDICATIONS FOR MEDICAL TREATMENT

Active medical treatment is indicated in all cases of active peptic ulcer. When healed lesions are encountered, judgment as to the dietary and other restrictions to be advised, if any, must be based on the duration of the remission and the various other factors present.

INDICATIONS FOR OPERATION

The indications for operation arise, in essence, from the complications of ulcer, the most urgent, of course, being acute perforation. Subacute and chronic perforations do not necessarily constitute indications. Massive hemorrhage is best treated medically at the time of hemorrhage, although in selected cases surgical attempts to tie off the bleeding artery or even to excise the lesion may properly be elected. In certain instances of recurring massive hemorrhage subtotal gastric resection in an interval between episodes of bleeding may be desirable. However, even subtotal gastrectomy does not guarantee against recurrent massive hemorrhage.⁴¹ The most frequent indication for operative treatment is stenosis. In my experience even stenosis does not necessarily require operation unless the stenotic lumen is reduced to a diameter of only 3 mm. or less as judged by fluoroscopic study. Gastric ulcer should be removed if there is serious question as to whether it is benign or malignant; this is of course the question unless it heals satisfactorily within reasonable time under medical treatment. Healing should be judged not from disappearance of symptoms but from objective roentgen and gastroscopic disappearance of the crater. Jejunal ulcer may be treated medically, although as a rule its management is more difficult than is that of primary gastric or duodenal ulcer, and hence operation may be in order. In the final analysis, it must be recognized that no medical or surgical procedure, except total gastrectomy, will regularly result in complete and permanent achlorhydria and that hence there is no method of therapy which regularly results in the complete and permanent cure of the disease peptic ulcer.

41. Kirsner, J. B., and Palmer, W. L.: The Treatment of Massive Hemorrhage from Peptic Ulcer, *Internat. Clin.* 4:105, 1939.

GASTROSCOPIC DIFFERENTIAL DIAGNOSIS OF BENIGN AND MALIGNANT ULCER OF THE STOMACH

AN ANALYSIS OF THE GASTROSCOPIC PICTURE OF ONE HUNDRED
AND THIRTY-THREE LESIONS

RUDOLF SCHINDLER, M.D.

CHICAGO

AND

O. ARNDAL, M.D.

GLENDALE, CALIF.

Because gastroscopy is a minor procedure that can be performed in the office and is carried out with no real discomfort to the patient when the proper technic is used, the gastroscopic method has been widely accepted within the last few years. Its value in the diagnosis of chronic gastroduodenal ulcer has been discussed thoroughly and repeatedly.¹ Therefore, only a brief summary of the chief facts will be given here.

Roentgen examination is superior to gastroscopy in the diagnosis of chronic gastroduodenal ulcer. The duodenal ulcer cannot be seen with the gastroscope. Benign ulcer of the pyloric ring cannot be seen with a gastroscope because the pylorus is drawn out of the visual field by adhesions. Some benign gastric ulcers of the lesser curvature of the antrum and of that small stripe of the posterior wall on which the gastroscope is lying escape detection with the gastroscopic method. Most gastric ulcers are seen clearly through a gastroscope, and there is a small but not unimportant group of gastric ulcers which escape even the most refined roentgen relief compression technic but which can readily be seen with a gastroscope. The healing process of benign gastric ulcer is best observed by a gastroscope. The condition of the mucosa surrounding the ulcer and at a distance from the ulcer can be determined only by gastroscopic observation.

The most important statement, however, about the usefulness of gastroscopy in cases of gastric ulcer is that gastroscopy is the best method for the differentiation of benign and malignant ulcer.

From the Department of Medicine, the University of Chicago.

1. Schindler, R.: (a) *Gastroscopy, the Endoscopic Study of Gastric Pathology*, Chicago, The University of Chicago Press, 1937; (b) *The Value of Gastroscopy in Diagnosis and Surgical Treatment of Chronic Gastroduodenal Ulcer*, *Surgery* 2:692, 1937.

It is the purpose of this paper to amplify and prove this statement by the analysis of the gastroscopic picture of 133 gastric ulcers in which the differential diagnosis had to be considered.

This differential diagnosis is considered to be difficult and often impossible. However, Palmer² came to the conclusion that "although there is no pathognomonic sign to indicate the benign nature of a lesion, the total evidence available from careful study permits the clinical differentiation of benign and malignant gastric ulcer with a high degree of accuracy." He came to this conclusion from clinical, roentgen and gastroscopic experience. As long as the opinion was prevalent that chronic gastric ulcer often undergoes carcinomatous transformation, the exact differential diagnosis was not so important from a practical viewpoint. Now more and more the conviction gains ground that benign ulcer rarely if ever precedes gastric carcinoma and that the two diseases are separate entities.³ If this is so, then the differential diagnosis becomes of the greatest practical importance. Delaying operation on resectable carcinoma by the so-called therapeutic test is hardly justified because in the waiting time the tumor may become inoperable. The resection of every benign ulcer is still less justified, as most ulcers can be treated medically. Resection has a definite mortality rate, and even the end results of such an operation are not always satisfactory.⁴ Every method, therefore, which permits improvement of the differentiation between these two lesions needs thorough consideration.

The facts that gastroscopy is superior in making the differential diagnosis between benign and malignant ulcer even to the inspection of the gross specimen and that it is equaled only by microscopic examination have been explained by the blood circulating in the living tissue which makes the gastroscopic picture plastic. Detailed discussion of this question has been given elsewhere.³ However, it was to be expected that gastroscopy, like any other diagnostic method, would not be infallible, and this expectation has been fulfilled. Gastroscopy is in a period of development, and every new experience adds new diagnostic criteria.

The important relation between the results of the gastroscopic and the roentgen method will not be discussed. This material is being collected by our roentgenologic collaborator, Dr. Frederic Templeton, and will be extensively presented by him. It may be mentioned that by

2. Palmer, W. L.: Benign and Malignant Ulcers: Their Relation and Clinical Differentiation, *Ann. Int. Med.* **13**:317, 1939.

3. Schindler, R.: Early Diagnosis of Cancer of the Stomach; Gastroscopy and Gastric Biopsy; Gastrophotography and X-Rays, *J. Nat. Cancer Inst.* **1**:451, 1941.

4. Schindler, R.: Gastroscopic Observations in Resected Stomach, *Am. J. Digest. Dis.* **7**:502, 1940.

roentgen examination the number of localized lesions seen is greater than that seen by gastroscopy. By gastroscopy 24 lesions were missed; but by roentgen examination only 16 lesions were overlooked. The number of wrong differential diagnoses is about the same with each method. By gastroscopy 6 lesions were wrongly diagnosed; by roentgen examination 9 wrong differential diagnoses were made. The chief difference, however, is in the number of indefinite diagnoses among the 113 gastric ulcers seen by gastroscopy. A noncommittal indefinite diagnosis was made in only 2 cases; but at roentgen examination in 15 cases no commitment was made. All these figures refer only to the first examination. Frequently, if there was nonagreement between the results of roentgen examination and of gastroscopy, the patient was reexamined by both methods, and the results obtained with the one method sometimes influenced the interpretation of the findings obtained by the other method decisively.

Although the results of gastroscopy were rather satisfactory in our series, we asked ourselves whether these cases could teach us a better evaluation of the picture observed at the gastroscopic examination and whether the number of wrong or indefinite gastroscopic differential diagnoses could still be reduced. This analysis concerned 113 gastric ulcers visualized gastroscopically, 79 of which proved to be benign ulcers, and 34, malignant. The final diagnosis was established in every case, either from the patient's recovery after medical treatment as proved by clinical observation and roentgen or gastroscopic reexamination or from microscopic sections after operation or autopsy. We tried to answer the following questions: 1. Which gastroscopic signs speak in favor of benign ulcer? 2. Which gastroscopic signs are not proof of benign ulcer? 3. Which gastroscopic signs speak in favor of malignant ulceration? 4. Which gastroscopic signs are not proof of malignant ulceration?

It is not within the scope of this paper to describe extensively the gastroscopic aspect of the normal or the pathologic gastric mucosa or to describe the common pictures of benign and malignant gastric ulcer. Such discussion will be found elsewhere.^{1a}

SIGNS IN FAVOR OF BENIGN ULCER

Perfectly Sharp Edge Without a Surrounding Wall.—Since in the gastroscopic picture, in contrast to the picture obtained in the gross specimen, the ulcer floor is a different color from that of the surrounding gastric mucosa, it usually is easy to state whether or not the edge of the ulceration is sharp and punched out or not. This sharpness of the edge must not be confused with a regular edge; as will be shown later, the edge of an ulcer can be irregular and still have a sharply cutout

appearance. In 72 of 79 cases of benign ulcer, the gastroscopic picture showed a punched-out lesion with perfectly sharp edges and no surrounding wall. All of these ulcers with the exception of 5 were located in the body of the stomach, and most of them in or near the lesser curvature above the angulus.⁵ Only 1 malignant ulcer in 34 cases had sharp edges, and this ulcer was located in the anterior wall of the antrum, close to the greater curvature. This case will be discussed separately. In some cases the huge wall of a tumor overlapped the edges of the ulcer so

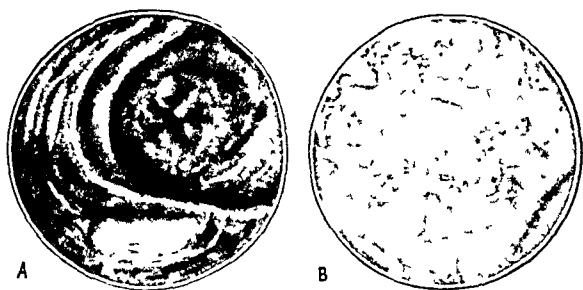


Fig. 1.—Gastroscopic views of a benign and a malignant ulcer: *A*, benign ulcer. In the background the closing pylorus is seen. The parabolic curve is the angulus. Immediately above the angulus, an ulcer is seen. Its sharp, punched-out margin and the smooth noninfiltrated adjacent mucosa are characteristic of benign ulcer. *B*, malignant ulcer. A portion of the angulus is seen at the right side of the picture. The ulcer seen above in the lesser curvature cannot possibly be benign because of the unsharp blending edge and the stiff nodular infiltration of the surrounding tissue.

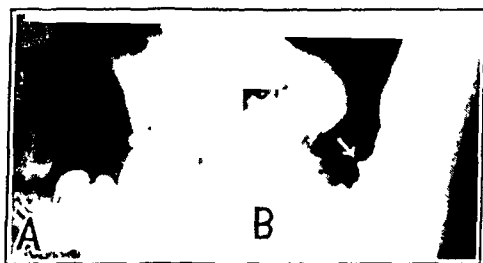


Fig. 2.—Roentgenograms of the 2 ulcers shown in figure 1. *A*, benign ulcer. Note the distance of the ulcer from the incisura angularis, which obviously is not identical with the angulus. *B*, malignant ulcer. A certain differential diagnosis from roentgen examination is not possible, although when observed gastroscopically, the difference between these 2 lesions is striking.

5. The terminology of the portions of the stomach follows the suggestions given in the textbooks of gastroscopy (Schindler, R.: *Lehrbuch und Atlas der Gastroskopie*, Munich, J. F. Lehmann, 1923; footnote 1 *a*). Gastroscopically, the stomach is definitely divided into two cavities, the body and the antrum; the musculus sphincter antri forms the dividing line between them. The angulus, which is located at the same level as the musculus sphincter antri, constitutes the bend of the lesser curvature from a caudad to a cephalad direction. It does not necessarily correspond with the incisura angularis of the roentgenologist (fig. 2).

much that their character could not be determined. But the nature of the wall in these cases made the diagnosis of malignant ulcer certain. Therefore, it might be said that the sharp edge of an ulcer is one of the best gastroscopic signs of benignity.

No Infiltration of the Mucosa Whatever.—Only in benign lesions did we see an entirely normal and noninfiltrated mucosa encircling a sharply limited punched-out ulceration. Such a normal mucosa was found in 26 out of 79 benign ulcers. This statement probably will surprise those familiar with the European studies concerning gastritis combined with gastric ulcer. It has been contended⁶ that inflammation is present in every case of gastric ulcer. However, gastroscopists have contended for a long time that this conception is wrong and that material obtained at operation contained artificial changes which had been misinterpreted.⁷ Baxmeier and one of us (R. S.)⁸ found that in ulcer-bearing stomachs inflammation was absent at all gastroscopic examinations in 47 per cent. The percentage obtained in the series presented in this paper is about 33 per cent. It is obvious that in contrast to Konjetzny's⁶ conceptions no inflammation will be found grossly in a rather high percentage of all benign ulcers. The lack of inflammation around the ulcer often will be decisive for the differential diagnosis. In a 57 year old physician, a huge ulcer crater had been found on roentgen examination immediately below the cardia and had been interpreted as probable carcinoma; but on gastroscopic examination the sharp edges and the perfectly normal gastric mucosa around the ulcer spoke in favor of a benign lesion. Therefore, medical treatment was advised. The niche disappeared, the patient recovered and at the time of writing is still alive two and one-half years after the gastroscopic examination.

Hemorrhages and Pigment Spots Lying in a Normal Mucosa Localized Gastric Purpura.—In the paper published by Baxmeier and one of us (R. S.), it was stated that mucosal hemorrhages and pigment spots in a normal mucosa are found much more frequently in patients with ulcer-bearing stomachs than in other patients with abdominal distress. The relation of these lesions to gastric ulcer has been described elsewhere.⁹ In our series we found them with 15 of 79 benign ulcers and with only 1 of 34 malignant ulcers. Therefore, their presence suggests

6. Konjetzny, G. E.: *Die entzündliche Grundlage der typischen Geschwürsbildung im Magen und Duodenum*, Berlin, Julius Springer, 1930.

7. Schindler, R.; Necheles, H., and Gold, R.: *Surgical Gastritis: A Study on the Genesis of Gastritis Found in Resected Stomachs with Particular Reference to the So-Called "Antral Gastritis," Associated with Ulcer*, Surg., Gynec. & Obst. **69**:281, 1939.

8. Schindler, R., and Baxmeier, R.: *Mucosal Changes Accompanying Gastric Ulcer*, Ann. Int. Med. **13**:693, 1939.

9. Schindler, R.: *Chronic Localized Gastric Purpura*, Am. J. Digest. Dis. **5**:796, 1939.

the benignity of an accompanying ulceration. This, however, is true only for the expert in gastroscopy. Mucosal hemorrhages lying in an inflamed mucosa are frequent in all types of inflammation and in our opinion have nothing to do with the lesions described as localized gastric purpura and with the formation of benign ulcer. The presence of hemorrhages and pigment spots can be used in favor of the diagnosis of benign ulcer only if the normal character of the mucosa in which they are lying is beyond any doubt. Of the 22 cases of benign ulcer visualized by roentgen examination but not seen gastroscopically, mucosal hemorrhages and pigment spots were seen in 4. Thus these lesions may be used as an indirect gastroscopic sign in favor of the benign nature of an ulcer seen only on roentgen examination.

Henning's Sign (Arch-Shaped Distortion of the Angulus).—The sign first described by Henning¹⁰ is usually produced by an ulcer immediately behind the angulus lying in the blind area of the lesser curvature of the antrum which causes the otherwise smoothly rounded angulus to look like a Gothic arch. In the true Henning sign the angulus shows no sign of ulceration or inflammatory infiltration. But it may be present in cases in which the ulcer lies proximal to the angulus also. This sign was present in 4 of the 79 benign ulcers, but it was not seen in the malignant ulcerations. It appears that in cases in which a niche demonstrated by roentgen examination remains invisible gastroscopically behind the angulus, the presence of the Henning sign speaks in favor of the benignity of the ulcer. The irregularity of the angulus produced by malignant infiltration can and must not be confused with the true Henning sign. The experienced gastroscopist, furthermore, will remember that sometimes crossing folds may simulate an arch-shaped appearance of the angulus and that this has no diagnostic significance whatever.

Hourglass Fold.—In cases of true organic hourglass stomach, which are rare, a fold of the greater curvature protrudes deeply into the cavity of the stomach. In some cases it is possible to direct the tip of the gastroscope into the lower bag of the hourglass, and then if the instrument is withdrawn, the large fold will become visible, crossing the greater curvature from the anterior to the posterior wall. Sometimes the fold crosses the anterior wall up to the location of the ulcer in the lesser curvature. This unmistakable picture, which we observed in 3 cases of benign ulcer, was not found in any case of malignant lesion. In the cases of malignant hourglass stomach we have seen, we were not able to pass the instrument into the lower bag.

10. Henning, N.: *Die Entzündung des Magens*, Leipzig, Johann Ambrosius Barth, 1934.

Converging Folds.—Converging folds are seen less frequently by gastroscopic than by roentgen examination,¹¹ especially when the ulcer is healing; and it seems that the folds observed only by roentgen examination have their origin in the scarring of the lower layers of the gastric wall. However, they are seen by gastroscopy also, radiating toward the margin of the ulcer. They were found to be present in 16 of 79 benign ulcers. Only in 1 malignant ulcer was a single fold seen to cross the anterior wall toward the margin of the ulcer, which was surrounded by an extremely high edematous wall. This case will be described in detail later.

SIGNS WHICH ARE NOT PROOF OF BENIGN ULCER

Normal Mucosa Distant from the Ulcer.—As we said before, sometimes there is no inflammation present with benign ulcer. According to the European literature¹² one would think that this would never occur with malignant ulcer, because there is almost unanimity that gastric carcinoma develops in a gastritic, usually atrophic, mucosa. This may be true for the mucosa immediately surrounding malignant ulcer, but in 5 of 34 malignant ulcers, perfectly normal mucosa was found distant from the lesion. An apparently normal mucosa may therefore be found in both malignant and benign ulcers and cannot be used for the differential diagnosis.

Uniform Color of the Wall and the Surrounding Mucosa.—As will be shown later, the contrast of the color of the wall and the surrounding mucosa is diagnostic for carcinoma. However, in 9 of 34 malignant ulcers, the wall surrounding the ulcer was the same orange red color as the surrounding mucosa, so that uniform color of the wall and the mucosa is no proof of the benign nature of a lesion.

Mucosal Islands Within the Ulcer.—Mucosal islands growing within the ulcer floor were seen in 3 of the 79 benign ulcers and in 1 of the 34 malignant ulcers. They cannot be used in favor of either diagnosis.

SIGNS WHICH SPEAK IN FAVOR OF MALIGNANT ULCER

Limiting Wall on One Side and Blending Infiltration on the Other Side.—If there is a blending of the color of the ulcer floor with the adjacent mucosa and on the other hand an elevated wall at the opposite side, then malignant ulcer can be diagnosed safely. This picture has not been seen in any of the 79 benign ulcers, but it was seen in 11 of the

11. Schindler, R., and Templeton, F.: Comparison of Gastroscopic and Roentgen Findings, *Radiology* 29:472, 1937.

12. Konjetzny, G. E.: *Der Magenkrebs*, Stuttgart, Ferdinand Enke, 1938.

34 malignant ulcers. This is the classic picture of a type 3 carcinoma according to Borrmann's macroscopic classification.¹³

Large Tumor Nodes and Masses in the Surroundings.—The malignant ulcers in our series were all surrounded by some form of infiltration. Large tumor nodes and masses surrounding an ulcer are suggestive of a malignant lesion. Six of 34 malignant ulcers presented this picture, but it is important to note that 1 benign ulcer among the 79 cases studied showed a similar picture. In this case the anterior edge of the ulcer was entirely sharp, but the posterior edge could not be seen as it was covered by a large red hemorrhagic node of the posterior wall, and many other nodes in the adjacent mucosa suggested definitely a malignant lesion. The course proved that this impression was wrong. The case will be discussed later.

Irregular Ridges or Nodes Within the Ulcer Floor.—Irregular ridges or nodes within the ulcer floor were seen in 4 malignant ulcers but in no benign ulcer. Emphasis, however, has to be laid on the word "irregular." If one sees the floor of a large ulcer consisting of many regular nodules, one is inclined to make the diagnosis of carcinoma. This mistake was made by one of us (R. S.) in one of his earliest observations, and the respective case was pictured and published.¹⁴ At that time the wrong diagnosis of carcinoma was made, but the following operation showed that the regular nodules were the lobuli of the pancreas, into which the ulcer had penetrated.

Diffuse Infiltration of the Whole Stomach, Even Without Visualization of the Ulcer.—Diffuse infiltration of the whole stomach, even without visualization of the ulcer, although encountered in only 1 case of malignant ulcer, is mentioned because of its great significance. Benign ulcer with considerable gastritis surrounding the lesion was diagnosed by roentgen examination, and for more than a year the clinical course was that of benign ulcer. However, at the first gastroscopic examination the whole gastric mucosa was seen to be stiffly infiltrated, although the ulcer itself never came into view. Malignant lesion was strongly suspected from this picture, but some rare kind of extensive hypertrophic gastritis or some other diffusely infiltrative lesion could not be excluded. At autopsy the entire stomach was stiffly infiltrated by carcinoma, and, retrospectively, it is entirely clear that diffusely infiltrative carcinoma was present from the beginning. In this case, the niche in the roentgenogram became small and almost disappeared during medical treatment;

13. Borrmann, R., in Henke, F., and Lubarsch, O.: *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1926, vol. 4, pt. 1, p. 865.

14. Schindler, R.: *Lehrbuch und Atlas der Gastroskopie*, Munich, J. F. Lehmann, 1923.

this misled the clinician. Perhaps it would not have been wise to have made the gastroscopic diagnosis of malignant lesion after the very first examination, but when the stiff nodular infiltration persisted through several reexaminations the malignant nature of the lesion should have been apparent.

White Crystal-Like Floating Material of the Ulcer Floor.—Pathologists¹³ have said that sometimes the floor of a malignant lesion is covered by necrotic dirty material which floats when held under a current of water. This floating may be observed by gastroscopy also when the stomach is inflated. But the material in such cases looks brilliant white and crystal-like. The floor of a benign ulcer may look brilliant white, too, and it may contain necrotic material, but the specific crystal-like floating appearance, according to our experience, is seen only in malignant ulcers.

Location in the Antrum Close to the Greater Curvature.—Some authors, especially Holmes and Hampton,¹⁵ have emphasized that most prepyloric ulcers are malignant. In our series, out of 34 malignant ulcers, 17 were located in the antrum or prepyloric region. Three ulcers were in the greater curvature of the antrum and 3 in the anterior wall close to the greater curvature. Only 1 malignant ulcer was located on the lesser curvature and the posterior wall of the antrum. In 10 cases a diffuse lesion of the whole antrum was seen.

Out of 79 benign ulcers, only 5 were found in the antrum or prepyloric region. Of these, 2 ulcers were found in the lesser curvature; 2 in the anterior wall; and only 1 close to the greater curvature. In 1 case the wrong diagnosis of benign ulcer was made at the first examination. Location close to the greater curvature, unusual shape and bleeding of the edge should have cautioned the observer. This case will be discussed later. In order to diagnose benign ulcer in the antrum gastroscopically with certainty, especially if the ulcer is not located within the lesser curvature, it must not be associated with any sign which might question its benign nature.

Visible Ulcer in the Pylorus.—Benign ulcer of the pylorus usually distorts the pylorus so that it is drawn out of the field of vision and cannot be observed at the gastroscopic examination. If an ulcer is seen to be located in the pylorus, it is most likely malignant. This rule proved to be correct in 1 case of extremely small carcinomatous ulcer of the pyloric ring. This case has been described elsewhere.¹⁶

Bleeding of the Edge.—Bleeding of the edge of a malignant ulcer may be observed frequently during gastroscopic examination. We saw

15. Holmes, G. W., and Hampton, A. O.: The Importance of the Location in the Differential Diagnosis of Benign and Malignant Ulcerations, New England J. Med. 208:971, 1933.

16. Schindler, R., and Gold, R.: Gastroscopy in Gastric Carcinoma, Especially in Its Early Diagnosis, Surg., Gynec. & Obst. 69:1, 1939.

this in 6 of our cases. The benign ulcer usually does not bleed at all. If it is seen bleeding, the blood is more likely to originate from the base of the floor and to cover the whole ulcer. However, also in 2 benign ulcers, bleeding of the edge was observed, so that this is not a reliable, although a suggestive, sign of malignancy.

Dark Red Color of the Wall and Pale Surroundings.—It has been stated before that in both benign and malignant ulcers a wall is often present which may have the same color as the adjacent mucosa. But in 7 malignant ulcers in our series, this surrounding wall was found to be strikingly dark red in contrast to the pale surrounding mucosa. In none of the 79 benign ulcers was this characteristic picture found.



Fig. 3.—Unusually large ulcer niche. The benign nature of the ulcer was proved by the clinical course and by microscopic examination after autopsy.

Blending Edge.—While the typical benign ulcer has sharp edges on all sides, the floor of the malignant ulcer blends smoothly with the adjacent mucosa so that either nowhere or at a large portion of the circumference no definite borderline between the ulcer floor and the mucosa can be made out (fig. 1 B). Some blending of the edge, however, was seen in 3 benign ulcers of the 79, but in all 3 the blending area was only a few millimeters wide. Nevertheless, in 2 of these cases, this sign led to the wrong diagnosis of malignant lesion. These cases will be discussed later. Although they have taught us that the blending of the ulcer edge is not an absolute sign, we still feel that in such cases the definite diagnosis of benign ulcer should not be made. We feel that in these few cases indefinite or even wrong gastroscopic diagnoses are unavoidable.

Ulcerations in the Wall Surrounding the Ulcer.—Small ulcerations in the surroundings of a benign ulcer are rare. In only 3 cases of benign ulcer such small ulcerations were seen in the adjacent mildly inflamed mucosa. Never was such a small ulcer seen within the wall surrounding a benign ulcer, although such erosions occurred within the walls of 3 malignant ulcers. We have the definite impression that ulcerations within the wall are diagnostic of malignant ulcer. In 1 of our cases the correct diagnosis was based exclusively on this sign.

GASTROSCOPIC SIGNS WHICH ARE NOT PROOF OF MALIGNANT ULCERATION

Large Size.—In our series we had such a great amount of unusually large benign ulcers that we feel that large size is not even suggestive of malignancy in doubtful cases. The base of our largest benign ulcer was 51 mm. in diameter. Not less than 12 of the benign ulcers had a base of 25 mm. or more. On the other hand, small ulcers were seen in cases of gastric carcinoma.

Atrophic Gastritis.—According to former conceptions about the frequent occurrence of atrophic gastritis with carcinoma and the absence of this disease with chronic gastric ulcer, we have been inclined to decide in favor of carcinoma when we saw gastroscopically extensive outspoken atrophy. We had to abandon this criterion because we found benign gastric ulcers in which the gastric mucosa was almost completely atrophic. Some kind of atrophy, either patchy or complete, was seen associated with 19 of the 79 benign ulcers.

Infiltration of the Mucosa About the Ulcer.—It has been mentioned before that benign ulcer is frequently surrounded by an area of infiltration or by a callous wall. Therefore, these findings cannot be used in favor of a diagnosis of carcinoma. The mucosa about a benign ulcer was seen to be definitely infiltrated in 13 instances.

Callous or Edematous Wall.—A true circular wall may be present in both types of lesion. Such a wall was seen in not less than 7 of our benign ulcers.

Ragged Edge.—The sign of ragged edge is listed here for the sake of completeness. It has been mentioned before that the ragged or irregular edge of an ulcer must not be confused with the blending of the ulcer floor with the surrounding mucosa. The latter sign is pretty characteristic of a malignant lesion, but a benign ulcer may have an irregular and even ragged edge; this, however, shows sharp limitation between the ulcerated area and the mucosa at every point (fig. 4). It may even occur that benign ulcer, which at the beginning is completely round or elliptic may in the later development send out irregular protuberances which seem to creep into the previously normal mucosa and effect a rather grotesque and unexpected picture, which is different

from what is usually seen by roentgen examination. At the first examination, 5 benign ulcers presented the ragged appearance described.

Hill-Like Elevated Area.—One of us (R. S.) previously described this sign as characteristic of malignant lesion. This opinion cannot be held any longer. If the ulcer presents the usual signs of benignity then its location on an elevation does not disprove the diagnosis. Three of our benign ulcers were found to be located on hill-like elevations.

Necrotic Material on the Ulcer Floor.—If the beginner sees large amounts of necrotic material covering the ulcer floor, he is much inclined to diagnose a malignant lesion. This, however, is not permissible. In



Fig. 4.—Gastroscopic view of a benign ulcer with a ragged edge. In spite of the stiff nodular infiltration of the surrounding mucosa and of the ragged edge, the benign nature of this ulcer can safely be diagnosed, because the edge of the ulcer is sharply cut out.



Fig. 5.—Gastroscopic view of an unusually large benign ulcer located on the lower posterior wall. To the beginner, the nodes of the floor would suggest a malignant lesion, but their regularity proves that they are the lobuli of the pancreas into which the ulcer has penetrated. Under medical care this ulcer healed completely within a few weeks.

cases of spastic retention necrotic food material sometimes is seen to be located on the floor of a benign ulcer. In our series this happened in 3 cases.

Regular Nodes of the Floor (Fig. 5.).—It has been mentioned before that former experience taught us that regular nodes of an ulcer floor may be the noduli of the pancreas into which the ulcer has penetrated. We found this sign in 1 case of our ulcer series, and it is listed here again because the beginner will regularly diagnose carcinoma when he sees this phenomenon.

ANALYSIS OF THE WRONG AND THE INDEFINITE GASTROSCOPIC DIAGNOSES

As mentioned before, in a series of 113 gastric ulcers visualized gastroscopically 6 wrong gastroscopic diagnoses were made, and in 2 cases no definite differential diagnosis was made. In the same series 7 wrong roentgen diagnoses were made, and in 15 cases no definite statement could be made after roentgen examination. In only 1 case both methods came to a wrong diagnosis.

The cases in which a wrong or indefinite diagnosis was made by gastroscopy will be reported briefly. The first 2 cases are cases in which a benign lesion was wrongly assumed to be present.

REPORT OF CASES

CASE 1.—It is important to note that in the one case in which the roentgen examination and the gastroscopic examination concurred in the wrong diagnosis of benign ulcer, the therapeutic procedure was not definitely influenced by this error. This case confirms Palmer's opinion that critical evaluation of all symptoms will lead practically always to correct therapy. The roentgenologist's impression was: "I doubt but cannot rule out the possibility of malignant lesion." The first gastroscopic protocol read as follows: "A large ulcer was seen in the anterior wall of the antrum at the level of the angulus. . . . It was not deep, but its diameter was at least 1.5 cm. The color of the floor was yellowish gray. The edge was perfectly sharp. At the lower portion of the ulcer toward the greater curvature there was a darkish red excavation within the floor of the ulcer. Small nodules surrounded the edge of the ulcer. The mucosa, however, did not show definite inflammatory changes. In the normal mucosa of the lesser curvature, 1 cm. above the ulcer, a small elliptic ulceration about 2 mm. long and about 1 mm. wide was seen. When the observation was continued, the anterior edge of the ulcer started bleeding spontaneously but only mildly. The other portions of the gastric mucosa were perfectly normal. In spite of the lavage of the evening before, a large amount of fluid containing food remnants and free hydrochloric acid was obtained."

In the impression the unusual shape and character of this sharply limited ulcer were emphasized. This, together with the clinical picture, led to careful observation of the patient, and three weeks later the gastroscopic impression was: "Today the ulcer looks carcinomatous. I believe this is a benign lesion, but the patient should be reexamined within a week because malignancy cannot be excluded absolutely, since it is amazing how the shape of this ulcer changed within a short time."

A definite wall-like elevation was seen at this time. After this report the patient was advised to undergo gastric resection. A rather small carcinoma with a large ulcer located in the antrum was found at operation, and successful resection was carried out. There can be little doubt that if we had applied the signs obtained from the previous analysis, either a correct or at least an indefinite diagnosis would have been made at the very first examination. The location of the ulcer in the antrum close to the greater curvature, the bleeding of the edge during the examination and the finding of a second small ulceration should have been interpreted in favor of the diagnosis of malignant lesion.

CASE 2.—In the second case in which a wrong gastroscopic diagnosis was made in favor of a benign lesion, the patient was a 55 year old man. At the first roentgen examination, the diagnosis was carcinoma. At a second examination the roentgenologist was unable to differentiate definitely between a benign and a malignant lesion. The gastroscopic impression was as follows: "The wall at the anterior side of the huge ulcer crater is higher than is usually seen in cases of benign ulcer. Nevertheless, the picture is not characteristic of a malignant lesion, and I believe that this may be a benign ulcer . . ."

The study of the gross specimen revealed why a wrong diagnosis was made by gastroscopy. It contained 2 ulcers; the second and smaller one had evidently been hidden behind the huge wall at the gastroscopic examination. The floor of this smaller ulcer consisted entirely of carcinomatous tissue, but in the greatest portion of the upper large ulcer there was no carcinoma visible, although some cords of carcinomatous cells were seen, especially at that margin which was directed toward the small carcinomatous ulcer. The impression was obtained that this large ulcer had been digested away from the carcinomatous tissue by hydrochloric acid, 90 units of which had been found in the gastric juice. It was unfortunate that a high wall hid the second ulcer and the carcinomatous infiltration. Even a biopsy taken during gastroscopy would have solved the problem only if accidentally a piece of the small region still showing carcinomatous infiltration had been cut out. In this case also clinical observation together with the unusual roentgen and gastroscopic reports led to the proper therapeutic procedure, namely, successful resection.

In the following cases the wrong diagnoses were made in favor of malignant lesion, but the lesion turned out to be benign ulcer.

CASE 3.—In this case an indefinite diagnosis was made after roentgen examination, but at the first gastroscopic examination the diagnosis of carcinomatous ulcer was made. The protocol read as follows: "A huge crater was seen in the lesser curvature above the angulus. There was a low wall toward the anterior wall of the stomach. The floor of the ulcer crater showed a dirty gray brown and reddish color and gray dirty necrotic material. A definite borderline between the ulceration and the gastric mucosa was not seen. The edges of the ulcer were bleeding. The surroundings were infiltrated. The impression was: There is carcinomatous ulcer, type 3 present. I do not believe this ulcer is benign." However, the indefinite roentgen diagnosis led to gastroscopic reexamination a week later. The protocol read as follows: "The necrotic material in the floor of the ulcer had disappeared. The floor now looked dirty gray, but the dirty gray ulcer was sharply limited toward the mucosa . . . The angulus was arch shaped. The impression was: (1) The ulcer looks entirely benign today. (2) Henning's sign of the angulus is present."

After that, the patient was treated medically, and the further course proved the ulcer to be benign. Probably the mistake made at the first examination was unavoidable. But it is characteristic how close cooperation between clinician, roentgenologist and gastroscopist avoids a wrong course of therapy. The doubts arising from the roentgen examination led to a second gastroscopy through which the definite diagnosis of a benign ulcer became possible.

CASE 4.—This is the first case which taught us that tremendous nodular infiltration may be found in a benign ulcer. At roentgen examination the definite diagnosis of benign ulcer was made. The gastroscopic protocol read as follows: "The ulcer was seen on the lesser curvature. It was a brilliant white area, the posterior edge of which was overlapped by a large red hemorrhagic node of

the posterior wall and never came into view during the entire examination. The anterior edge was entirely sharp. In its surroundings many thick nodes were observed. The entrance to the antrum was oval shaped, narrow, slitlike and stiff. It could be moved by pressure on the abdominal wall but was not pliable . . . The impression was: There is an ulcer above the angulus, the anterior edge of which is sharp, but the entire circumference is never seen. There is tremendous thickening and stiffening of the antrum. This may be unusually severe inflammatory infiltration. However, it looks much more like submucous malignant infiltration or some other type of infiltrative process."

We have listed this case as involving a wrong gastroscopic diagnosis, but the protocol makes it clear that the picture was a most unusual one. The roentgen diagnosis of benign ulcer together with the gastroscopic observations of an unusual picture led to medical therapy, and at the following gastroscopic examinations the infiltration had disappeared, and the ulcer was readily recognized as benign. In this case now we should make a more indefinite diagnosis than we did in the protocol of the first gastroscopic examination.

CASE 5.—This case is remarkable because in it a greater number of gastroscopic examinations revealed continuously changing unusual pictures and because at a time when at gastroscopy the ulcer began to look entirely benign, the roentgenologist was inclined to change his diagnosis of benign ulcer to that of malignant ulcer. The gastroscopic picture in the beginning was such that even applying the criteria gained by our analysis would not have been sufficient to prevent a wrong diagnosis. The gastroscopic protocol read as follows: "Above the angulus on the lesser curvature a crater-like punched-out ulceration was seen. Its diameter was 1.5 cm. The floor was smooth and gray white. Its edge was entirely sharp toward the anterior wall, the posterior wall and the cardia. But in a small area toward the pylorus, we were unable to detect a sharp limitation between the ulcer and the surrounding mucosa. The ulcer edge was not ragged, and the ulcer floor was definitely blending with the surrounding mucosa, though only at one point about 3 mm. wide. The surrounding mucosa, especially toward the anterior wall, was swollen and reddened. At the posterior side a protruding wall was observed. This wall was neither soft, velvety, nor edematous, but stiffly infiltrated and cast a shadow on the posterior wall at the upper edge. At the point where the upper edge of the wall touched the lesser curvature, about 2 cm. above the ulcer crater, 2 whitish ulcers were seen lying in an inflamed mucosa. . . . The impression was: "A crater-like ulcer of the lesser curvature is present which I am forced to call malignant." This ulcer, observed for more than two years at the time of writing by numerous roentgen and gastroscopic examinations, never healed completely. Its shape changed in the most peculiar way. Islands of the mucosa developed in its floor, and disappeared again. The course seems to prove that this was benign ulcer of an unusual type, although it seems necessary to watch this patient carefully.

CASE 6.—This is the only case in which the wrong gastroscopic diagnosis of carcinoma led to operation. The case is remarkable because the patient had histamine-proved anacidity (single examination)¹⁷ and at gastroscopy, almost com-

17. Palmer, W. L.; Kirsner, J. B., and Nutter, P. B.: Spontaneous Variations in Gastric Secretion in Response to Histamine Stimulation, *Am. J. Digest. Dis.* 7:427, 1940. Palmer, W. L., and Nutter, P. B.: Peptic Ulcer and Achlorhydria, *Arch. Int. Med.* 65:499 (March) 1940.

plete atrophic gastritis. The latter observation together with large ulceration of the posterior wall led to the wrong diagnosis of carcinomatous ulcer. The department of pathology of the Mayo Clinic made a careful examination of the microscopic material of this ulcer. The ulcer proved to be perfectly benign. Since we now know that extensive atrophic gastritis is compatible with the presence of benign ulcer, today we probably should not commit ourselves and should make an indefinite diagnosis.

In the 2 following cases an indefinite diagnosis was made at gastroscopic examination.

CASE 7.—At roentgen examination the following statement was made: "Gastric ulcer is present. If this ulcer is benign, there is considerable associated gastritis." The gastroscopic impression was: "1. There is an ulcer crater of the lesser curvature with a high nodular wall. 2. There is hypertrophic gastritis. 3. I am unable to differentiate between benign and malignant ulcer and advise reexamination." A month later the reexamination advised was carried out, and the impression was: "Although the ulcer looks benign, I am still not ready to exclude malignancy because of the unusually high and stiff nodular wall." In spite of these indefinite roentgen and gastroscopic diagnoses, medical therapy was instituted and led to the recovery of the patient.

CASE 8.—After roentgen examination the statement was made: "The shallowness of the ulcer suggests that this lesion may be malignant." The gastroscopic impression was: "I cannot commit myself definitely on this ulcer. Its aspect is that of a benign ulcer, but the stiff infiltration of its anterior border, which is extensive, does not look like the callous wall of a benign ulcer and suggests a malignant lesion. There is extensive atrophic gastritis of the upper portion of the stomach."

This patient had carcinoma of the cervix treated by radium and roentgen therapy with good results. It seems that the gastric ulcer was benign. However, the patient failed to return after four months of observation, so that no definite, final diagnosis could be made. But it seems fair to place this case among those in which there were wrong and indefinite diagnoses.

According to our present experience we probably would now make correct diagnoses in 2 of these cases. In 2 of them we would make an indefinite diagnosis. But probably in 4 a wrong diagnosis would still be made. Thus we have to admit that with our present experience there would still be 6 of 113 ulcers of which a definite correct differential diagnosis could not be made. By roentgen examination, however, the diagnosis in 22 cases was either incorrect or indefinite. The patient will profit most by the use of both methods, and we believe that if this procedure is applied in every case, then in practically no case will the correct diagnosis be missed.

SUMMARY

The gastroscopic symptomatology of 113 gastric ulcers has been analyzed; 79 of these were benign and 34 malignant. Although it must be admitted that in 6 of the 113 cases of ulcer a definite correct diagnosis could not be made by gastroscopy even now, the value of the procedure is obvious.

CRITERIA OF AN ACCEPTABLE OPERATION FOR ULCER

THE IMPORTANCE OF THE ACID FACTOR

OWEN H. WANGENSTEEN, M.D.

AND

BERNARD LANNIN, M.D.

MINNEAPOLIS

The empiric surgical approach to the ulcer problem has come to an end. Out of fifty years of accumulated experience has come a mass of conflicting data with reference to the accomplishment of operation in the management of ulcer without a clearcut definition of the criteria of an acceptable operation. The cause of this confusion is not difficult to detect. There being no general agreement among clinicians or investigators concerning the cause of ulcer, the surgeon knew only that the objective of his craftsmanship was to prevent recurrence of ulcer; in determining how to attain that end, he had little or no help to guide him. Little wonder that the surgeon groped about aimlessly for procedures which he hoped might accomplish his objective of obviating recurrence of ulcer since he did not know how ulcer came about, what was demanded of a satisfactory operation or how his handicraft mediated its influence.

All this has changed. Accumulating evidence indicates clearly that acid is the important factor in the genesis of ulcer. It is not known what are the factors that condition the capacity of the gastric mechanism to secrete acid or what other factors may thwart or favor digestion of tissue by acid. However, that unneutralized hydrochloric acid secreted by the stomach may bring about the formation of ulcer is definitely established.

Bickel (1909),¹ Exalto (1911),² Langenskjöld (1914)³ and Mann and Williamson (1923)⁴ demonstrated successively that exclusion of

From the Department of Surgery, University of Minnesota Medical School.

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1. Bickel, A.: *Beobachtungen an Hunden mit exstirpiertem Duodenum*, Berl. klin. Wchnschr. **46**:1201-1202, 1909.

(Footnotes continued on next page)

the bile and the pancreatic juice from entry into the duodenum at the usual site was an effective means of producing ulcer. The Mann-Williamson operation of diverting bile and pancreatic juice into a lower level of the intestine has become an effective agency of producing ulcer and of indicating the great importance of the acid factor in the origin of ulcer. By the interposition of a valve which prevented retrograde regurgitation of the contents of the transplanted segment into which bile and pancreatic juice are dumped, Matthews and Dragstedt⁵ were able to bring about the formation of ulcer with performance of the Mann-Williamson operation at the new gastrojejunal outlet in 100 per cent of their experiments.

PRODUCTION OF ULCER BY THE STIMULATION OF GASTRIC SECRETION WITH HISTAMINE

With Code's⁶ method of the intramuscular implantation of histamine in beeswax (to permit gradual liberation of the histamine), ulcer has been produced in this laboratory in a large number of animals. Histamine is a powerful stimulant of gastric secretion and apparently exerts its effect directly on the parietal cells responsible for the secretion of acid. Under the influence of the abnormal torrent of acid gastric juice provoked by the continuous and gradual release of histamine from the beeswax, the agencies which succeed ordinarily in achieving intestinal chyme with a neutral p_H in the upper reaches of the jejunum are outdone, and acid digestion of the stomach and/or the duodenum ensues with the formation of one or more ulcers.⁷ These ulcers are similar in appearance to ulcers developing spontaneously in man. Hemorrhage, excavation, induration and perforation are common accompaniments. The experimental pro-

2. Exalto, J.: *Ulcus jejuni nach Gastroenterostomie*, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **23**:13-41, 1911.

3. Langenskjöld, F.: *Ueber die Widerstandsfähigkeit einiger lobender Gewebe gegen die Einwirkung eiweisspaltender Enzyme*, Skandinav. Arch. f. Physiol. **31**: 1-74, 1914.

4. Mann, F. C., and Williamson, C. S.: *The Experimental Production of Peptic Ulcer*, Ann. Surg. **77**:409-422, 1923.

5. Matthews, W. B., and Dragstedt, L. R.: *The Etiology of Gastric and Duodenal Ulcer*, Surg., Gynec. & Obst. **55**:265-286, 1932.

6. Code, C. F., and Varco, R. L.: *Chronic Histamine Action*, Proc. Soc. Exper. Biol. & Med. **44**:475-477, 1940.

7. Hay, L. J.; Varco, R. L.; Code, C. F., and Wangenstein, O. H.: *The Experimental Production of Gastric and Duodenal Ulcer in Laboratory Animals by the Intramuscular Injection of Histamine in Beeswax*, Surg., Gynec. & Obst., to be published. Walpole, S. H.; Varco, R. L.; Code, C. F., and Wangenstein, O. H.: *Production of Gastric and Duodenal Ulcers in the Cat by Intramuscular Implantation of Histamine*, Proc. Soc. Exper. Biol. & Med. **44**:619-621, 1940.

duction of ulcer by this means has served not alone to emphasize the great importance of acid in the genesis of ulcer; in addition, the method provides a simple means of producing ulcer in a variety of animals in which the development of ulcer may be studied together with factors which favor or retard the inception of ulcer as well as factors which favor or retard healing.

INFLUENCE OF FOOD RETENTION IN THE STOMACH ON THE PRODUCTION OF ULCER

It is to be recalled that ulcer develops spontaneously in man. As far as is known, at least in the common domestic or laboratory animals, spontaneous ulcer occurs by no means frequently. One of the factors which may bear on this issue is the rate of transit of food from the stomach. The human stomach is empty, normally, about seven hours after eating. The stomach of many laboratory animals cannot be relied on to be empty after twenty-four hours of starvation. The rabbit is a notable example. After days of starvation there may be food in the rabbit's stomach. The rabbit is one of the laboratory animals in which we have had difficulty in producing an ulcer with histamine in beeswax. More recently, by feeding 2 rabbits the pressed juice of ground carrots, cabbage and lettuce, we were successful in producing a large perforated duodenal ulcer in 1 (fig. 1 *D*). In the other rabbit, a large perforation involving a good portion of the entire length of the greater curvature of the stomach occurred. The experiments of Dragstedt suggested strongly the great neutralizing effect of food on gastric acidity. Dragstedt and Vaughn (1924)⁸ failed to note evidence of the digestion of viscera implanted with an intact blood supply into the entire stomach of a dog. When, however, Matthews and Dragstedt (1932) implanted such viscera into isolated gastric pouches of dogs, into which food could not enter, digestion of the implanted living tissue occurred regularly.

The traumatizing effect of food in provoking gastric erosion has been overemphasized and the neutralizing effect of food on gastric acidity has not been emphasized enough. The acid factor is far more important in the genesis of ulcer than mechanical trauma by food.

METHOD

Since acid appears to be the most important factor in the genesis of ulcer, it is logical to infer that effective reduction of gastric acidity should be the first requirement of a satisfactory operation directed at the surgical relief of ulcer.

8. Dragstedt, L. R., and Vaughn, A. M.: Gastric Ulcer Studies: The Resistance of Various Tissues to Gastric Digestion, *Arch. Surg.* 8:791-810 (May) 1924.

We have looked on the attainment of achlorhydria (absence of free hydrochloric acid) as a desirable objective after operation, feeling that achlorhydria is incompatible with recurrence of ulcer. In this study no patient has been considered postoperatively achlorhydric unless free hydrochloric acid was absent in the gastric aspirations after three successive subcutaneous injections of 0.5 mg. of histamine hydrochloride.⁹

Gastric acidity was determined by the usual colorimetric titration; Töpfer's reagent was employed as the end point for free hydrochloric acid. We have come more and more to disregard the determination for total acidity as having any real significance. As was pointed out previously, the reading for total acidity includes also the capacity of protein to combine with a base, e. g., sodium hydroxide; in

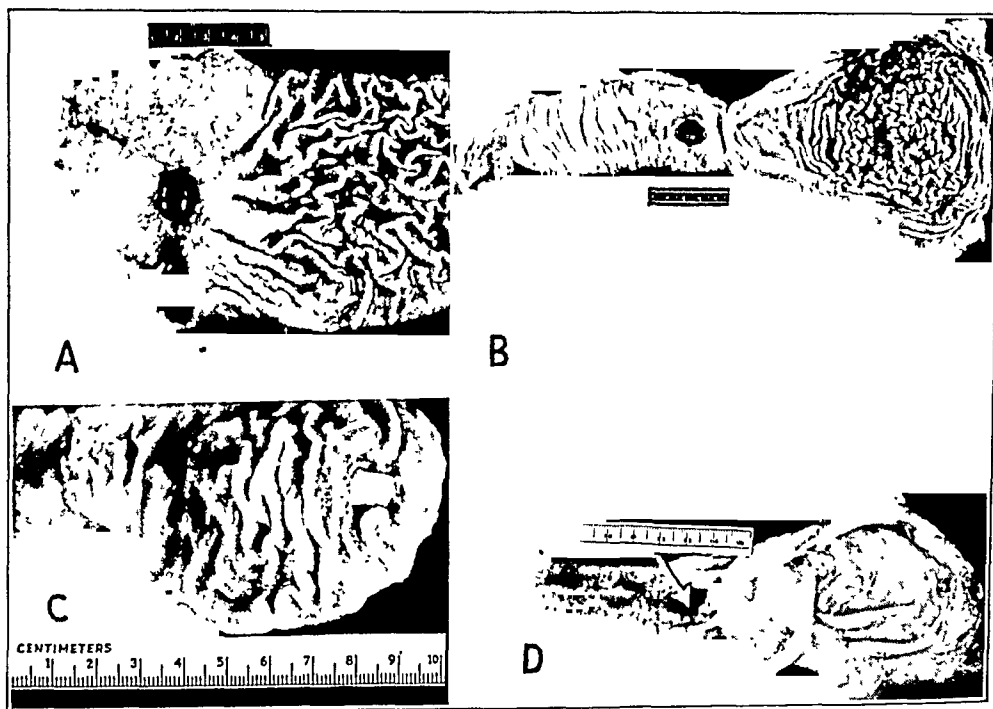


Fig. 1.—Ulcers in man and laboratory animals: *A*, spontaneous ulcer in man (resection specimen). The ulcer, perforating in type, caused serious hemorrhage in the antrum. *B*, ulcer produced in the duodenum of a dog by the intramuscular injection of histamine in beeswax. *C*, perforated gastric ulcer produced in a cat in the same manner. The gauze on the serous surface of the stomach can be seen plainly through the large perforation. *D*, perforated ulcer of the duodenum (at arrow) produced in a rabbit by the intramuscular injection of histamine in beeswax. The rabbit was fed the pressed juice of cabbage, carrots and lettuce.

consequence, the determination of total acids includes not alone the acid combined with protein but as well the buffering ability of the protein.

9. Wangenstein, O. H.; Varco, R. L.; Hay, L. J.; Walpole, S., and Trach, B.: Gastric Acidity Before and After Operative Procedure with Special Reference to the Role of the Pylorus and Antrum: A Preliminary Report of a Clinical and Experimental Study, *Ann. Surg.* **112**:626-670, 1940.

Gastric acidity was determined regularly in the morning before the patient had breakfast. A no. 14F duodenal tube with four perforations at the tip was introduced through the nose into the stomach. Continuous aspiration with the usual water suction siphonage apparatus was used through the period of the study. The following determinations were made at thirty minute intervals: (1) fasting; (2) after three successive subcutaneous injections of 0.5 mg. of histamine hydrochloride, each injection being made at intervals of thirty minutes. In an earlier study, the response to food and alcohol was elicited as well. Each test, as outlined, required that the patient remain for two hours. In the interests of conserving our own time, as well as that of the patients, we have come to rely largely on determinations of the fasting acidity (free hydrochloric acid) and the response to maximal stimulation with histamine (three successive subcutaneous injections of 0.5 mg. of histamine hydrochloride). These tests are performed frequently—when the patient leaves the hospital after operation (usually about the twelfth day) and again at intervals of six to eight weeks for the first six months and, thereafter, at three to four month intervals for an indefinite period.

The gastric emptying time (determined by the time required for complete gastric evacuation of 5 ounces [147.9 cc.] of ingested barium sulfate) has been followed in these patients. It is to be remembered, however, that, as indicated in an earlier study, the gastric emptying time is shortened almost invariably by all operations on the stomach.⁹ In this study, therefore, no reference will be made to that aspect of the problem. Most of the patients have been subjected to postoperative gastroscopic studies, but these data have not been surveyed completely as yet. This study concerns itself largely, therefore, with the determination of which operations for ulcer are attended by effective reduction of gastric acidity.

EVALUATION OF OPERATIVE PROCEDURES ON THE BASIS OF THE EFFECTIVE REDUCTION OF GASTRIC ACIDITY

The types of operation evaluated and a summary of the results of the study are given in the table. It is to be noted that consistent achlorhydria to triple stimulation with histamine was not achieved after any type of operation. Judged on the basis of effective reduction of gastric acidity, there are essentially only two types of operation which appear to afford real promise of thwarting the acid-ulcer diathesis, viz., those done on the patients in groups 3 and 4 *A*. Gastrojejunal ulcer has not been observed after either of these procedures. Accepting attainment of achlorhydria as an important criterion of a satisfactory operation for ulcer, the remaining types of operative procedure must be rejected as unsatisfactory because they fail to meet the requirements of the test too consistently. Further, in groups 1, 2, 4 and 5, the incidence of gastrojejunal ulcer alone constitutes adequate reason not to recommend these procedures.

Patients who have undergone the three-quarter gastric resection performed on the patients of groups 3 or 4 *A* may eat anything; the imposition of dietary restrictions is unnecessary. Within four months after operation, usually, the gastric capacity of the majority of these patients has returned to normal, so that they can eat a full-sized holiday

dinner without distress. It is to be remembered that the thin-walled fundus is the most dilatable portion of the stomach. In the main, most of these patients hold their weight satisfactorily. A number gain weight. Some patients, who through years of rigid dieting have cultivated an aversion for dairy products, tend to lose a little weight. If such patients exhibit substandard weights, they are given a 3,000 calory diet slip and instructed that while they may eat anything, they should choose their articles of diet largely according to that guide.

The majority of our patients come from the rural areas of Minnesota and earn their livelihood by the toil of their hands. It is a real pleasure

Types of Operation for Ulcer and Postoperative Incidence of Achlorhydria and Gastrojejunal Ulcer

Group	Type of Operation	Patients	Patients Consistently Achlorhydric to Triple Stimulation with Histamine	Gastrojejunal Ulcer
1	Gastrojejunostomy	29	0	10%*
2	Antral excision, or the small gastric excision, with Polya anastomosis.....	6	0	2 (33%)
3	Three-quarter resection, including the pylorus and antrum with Hofmeister retrocolic anastomosis	52	52 (63%)	0
1	Finsterer exclusion operation, three-quarter resection, allowing 2 to 3 finger-breadths of the antrum to remain....	12	3 (25%)	1 (8.5%)
4A	Finsterer exclusion operation with excision of the remnant of the antral mucosa	11	7 (63%)	0
5	Total intragastric regurgitation (Schmidlinsky operation) after antral excision	3	0	2 (66%)
6	Tubular excision of the greater curvature (fundusectomy) with gastrojejunostomy	8	2 (25%)	0
7	Tubular excision of the greater curvature (fundusectomy) without gastrojejunostomy	5	0	0

* Only 29 patients were submitted to study after triple stimulation with histamine. In 138 patients who had gastrojejunostomy, gastrojejunal ulcer was observed in 14.

to observe the large number of these patients who despite years of inability to be economically self-sufficient because of inadequate relief on conservative ulcer management become rehabilitated completely by being rid of their ulcer diathesis by a satisfactory operation.

There are a few persons who are not constituted to admit subjective improvement after any therapeutic procedure, let alone operation, however much their objective gain in health belies their statements. In this series (groups 3 and 4 A) we observed 2 patients of this sort. Both of these men looked fit. Both, however, had long backgrounds of psychoneurosis. After operative relief from the physical suffering of ulcer, patients of this type need continued encouragement and reassurance to diminish their mental distress. Occasional occurrences of this sort emphasize the obligation not alone to be alert to detect evidences of

psychopathic personality in patients but also to continue the friendly ministrations of the physician.

No evidence of anemia or dietary deficiency has been observed in patients on whom the three-quarter gastric resection has been performed. Inasmuch as Castle (1941)¹⁰ found that the fundus of the human stomach contains the intrinsic antianemic factor in abundance, it is not likely that anemia will follow such operations. Whether such patients will need particular notice with regard to iron and calcium requirements remains to be determined.

Our clinical experience suggests that the operative risk of the three-quarter resection for ulcer is between 2 and 3 per cent¹¹—a mortality rate no greater apparently than that reported by other investigators employing the small antral resection, or the operation used on the patients in group 2. Every one will admit freely that there is no object

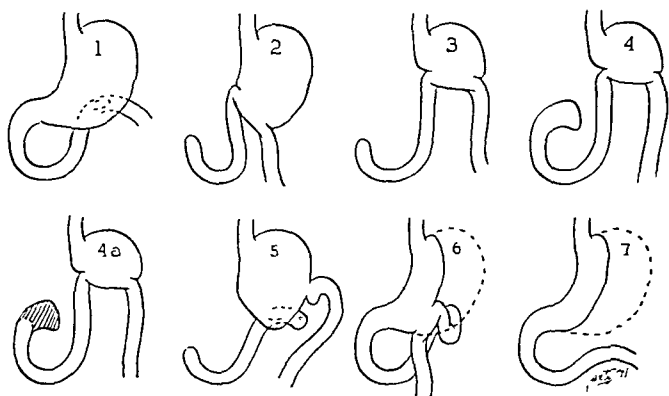


Fig. 2.—The various types of operative procedures performed on the patients in this study.

in excising more gastric tissue than is necessary to protect against recurrence of ulcer. The three-quarter resection satisfies this important requirement of an acceptable operation for ulcer; the operation used on the patients in group 2 does not. Whether resections intermediate in size will do away with the ulcer diathesis has not been determined. It has been pointed out before that even the three-quarter resection fails to make all patients uniformly achlorhydric to histamine stimulation.

In the surgical management of ulcer, it is to be remembered that the ulcer itself is not the disease but that it is only the end effect of unneutralized hydrochloric acid digesting away the wall of the stomach or the duodenum. It is the active gastric secretory mechanism which is respon-

10. Castle, W. B.: Stomach and Anemia, University of Minnesota Center for Continuation Study, March 1941.

11. Wangensteen, O. H.: The Surgeon and the Ulcer Problem, Illinois M. J. 80:100-110, 1941.

sible for the ulcer diathesis. Failure of operation to depress gastric secretion effectually compromises seriously the likelihood of the success of the procedure. There would appear to be some room for discriminating and effective choice among operations for ulcer, but there is little option between an acceptable operation and one which fails to meet the requirements of a satisfactory operation.

OBSERVATIONS CONCERNING THE VALIDITY OF THE EDKINS HYPOTHESIS

The operations outlined afforded an opportunity to submit Edkins' hypothesis (1906)¹² of pyloroantral control of gastric secretion to experimental scrutiny. It is to be noted that excision of the antrum (the operation done on the patients in group 2) fails to make patients achlorhydric. It was followed by gastrojejunal ulcer in 2 of the patients studied. Small gastric resections were done mostly as emergency operations for bleeding duodenal ulcer. During the last two years, the three-quarter gastric resection has been done under similar circumstances. The operation done on the patients in group 6 (fig. 2), in which the antrum is left, is not followed by a high incidence of persistent achlorhydria to triple stimulation with histamine. The satisfactory experience with operations done on the patients in groups 3 and 4 *A*, in which excision of the antrum accompanies extensive gastric resection, has been pointed out already. On the contrary, our experience with the operation performed on the patients in group 4, which differs from that done on the patients in group 4 *A* only in that the antral mucosa is excised in the latter, has been disappointing.

Case 1 throws interesting light on the relation of the antral mucosa to gastric secretion:

REPORT OF CASES

CASE 1.—E. H., a 42 year old man, was admitted to University Hospitals on April 1, 1940 with a typical history of duodenal ulcer of fourteen years' duration. For two years, the patient had been incapacitated by pain and unable to work. For eight months prior to admission, he had been subjected to a strict medical regimen which included administration of a colloidal suspension of aluminum hydroxide and medication with phenobarbital, without material improvement. There had been no antecedent perforation or massive hemorrhage.

On physical examination, there was evidence of slight exophthalmos, but the basal metabolic rate was normal. On gastric analysis, free acid was 90 degrees in the fasting specimen and 112, 122 and 110 degrees, respectively, in specimens taken thirty, sixty and ninety minutes after the injection of 0.5 mg. of histamine. On roentgen examination, a defect typical of duodenal ulcer was found. On April 3, a Finsterer antral exclusion operation with extensive (three-quarter) gastric resection (group 4) was performed. Three fingerbreadths of the antrum

12. Edkins, J. S.: The Chemical Mechanism of Gastric Secretion, *J. Physiol.* 34:133, 1906.

proximal to the pyloric sphincter was allowed to remain. The size of the resected gastric segment was 301 sq. cm. Closed (aseptic) anastomosis of the Hofmeister type was made. Convalescence was uneventful, and the patient left the hospital fifteen days after operation.

The patient was followed in the outpatient department. Epigastric pain recurred and was most severe at night. Over a period of ten weeks, gastric analysis was performed on four occasions, and free hydrochloric acid was found each time, once as high as 56 degrees with histamine stimulation.

Roentgen examination failed to reveal any evidence of gastrojejunal ulcer. On gastroscopic examination, several areas of erosion were detectable. It was believed that these were due to sloughing of the interrupted silk sutures in the inner row. (In the last twenty months, a running suture of catgut has been used for the inner row in all gastric resections. The outer row, however, is constituted of interrupted Halsted mattress sutures of fine silk.) Because of the persistence of symptoms and the continued presence of free hydrochloric acid in the gastric juice, the patient was admitted for excision of the residual antral segment. This operation was done on October 10. Closure of the duodenum was difficult. Temporary duodenal fistula developed, and this prolonged the hospital stay. On November 26, the patient was dismissed. In the early months of convalescence, free hydrochloric acid was found three times by gastric analysis; the highest value was 24 degrees and the average 12 degrees.

At the time of writing, the patient has been consistently achlorhydric (on three occasions during the past nine months), even to maximal stimulation with histamine (three successive doses of 0.5 mg. of histamine given at half hour intervals). The patient has been asymptotically free from distress, and gastroscopic and roentgen examinations fail to disclose any evidence of recurrent ulcer.

Summary.—A man 42 years of age with a history of duodenal ulcer of fourteen years' duration was submitted to the Finsterer exclusion operation. He failed to become achlorhydric and continued to have symptoms. After excision of the antral segment and the pylorus together with a small fragment of the duodenum (the area of the entire mucosal segment excised was only 24 sq. cm.), the patient has remained achlorhydric and has become symptom free. Objectively, no trace of recurrent ulcer remains.

This occurrence speaks significantly for the presence of a pyloro-antral hormone. In the portion of the antrum removed in the first operation, Dr. Robert E. Hebbel, pathologist in University Hospitals, described the presence of extensive antral gastritis. There was dense interstitial lymphocytic infiltration of the mucosa. It is significant that in the antral segment removed at the second operation (six months later) all evidence of interstitial mucosal antral gastritis had disappeared.

This patient (case 1) exhibited no objective evidence of gastrojejunal ulcer after the first operation. In another patient (case 2), however, gastrojejunal ulcer developed after the Finsterer exclusion operation.

CASE 2.—T. B., a man 40 years of age, was subjected to the Finsterer exclusion operation (group 4). Demonstrated gastrojejunal ulcer developed (table). Three months later the residual antral segment was excised. The area of the mucosal antral segment was 16 sq. cm. Achlorhydria did not develop. Hemorrhages from the gastrojejunal ulcer continued.

Three months after the second operation and six months after the initial Finsterer exclusion operation (Nov. 18, 1940), gastric resection was done in which the gastroduodenal ulcer was excised. The patient became achlorhydric at once and has continued symptomatically well.

It is needless to relate that we have ceased to use the Finsterer exclusion operation (group 4).

HISTAMINE CONTENT OF GASTRIC MUCOSA IN MAN

Gavin, McHenry and Wilson (1933)¹³ studied the histamine content of the gastric mucosa in the dog and observed that the fundic mucosa is richer in histamine than that of the pylorus. They concluded that 80 per cent of total histamine content of the dog's stomach is to be found in the pylorus. Code and Trach¹⁴ studied the histamine content in the mucosa of human stomachs resected for ulcer or carcinoma, making comparisons between the histamine content of the antral and the fundic mucosa. In cases of carcinoma of the stomach, sections of mucosa were dissected off the underlying muscle for study in areas where the gross appearance of the mucosa was fairly normal.

No significant differences in the histamine content of the gastric mucosa were observed in patients with ulcer or carcinoma of the stomach. Per unit of weight of tissue, the histamine content of the fundic mucosa exceeded that of the antrum. Subcutaneous injection of these mucosal extracts into dogs with prepared gastric pouches elicited somewhat comparable responses; in the main, the antral mucosal extracts produced the greater effect.

These observations of Code and Trach, when correlated with those made concerning the validity of the Edkins hypothesis based on the data concerning the operations done on the patients in groups 2, 4, 4A and 6, suggest that the antral mucosa may contain a hormonal stimulant of gastric secretion other than histamine. Certain it is that excision of the antrum is necessary to achieve consistent achlorhydria after the three-quarter gastric resection in man.

PROTECTIVE INFLUENCE OF OPERATIVE PROCEDURE AGAINST THE HISTAMINE-PRODUCED ULCER

We propose to submit all the operative procedures described, which are designed to alleviate ulcer in man, to experimental scrutiny, employing the histamine in beeswax method of producing ulcer in dogs. As yet,

13. Gavin, G.; McHenry, E. W., and Wilson, M. J.: Histamine in Canine Gastric Tissues, *J. Physiol.* **79**:234-238, 1933.

14. Code, C. F.; Trach, B., and Wangenstein, O. H.: The Histamine Content of Gastric Mucosa, unpublished data.

we have had occasion to assess the results of only three operative procedures, viz., those used in groups 1, 2 (fig. 3) and 3. The intramuscular implantation of histamine in beeswax following the performance of the operation used in group 1 or 2 is regularly attended by anastomotic ulcer in the dog; on the contrary, such anastomotic ulcer has not followed the operation used in group 3 after the administration of histamine in beeswax. This phase of the study is still in progress, and a complete report cannot be made at this time. The preliminary observations appear to corroborate the findings of the more complete study on patients with reference to the merit of operations in effectually reducing gastric acidity.

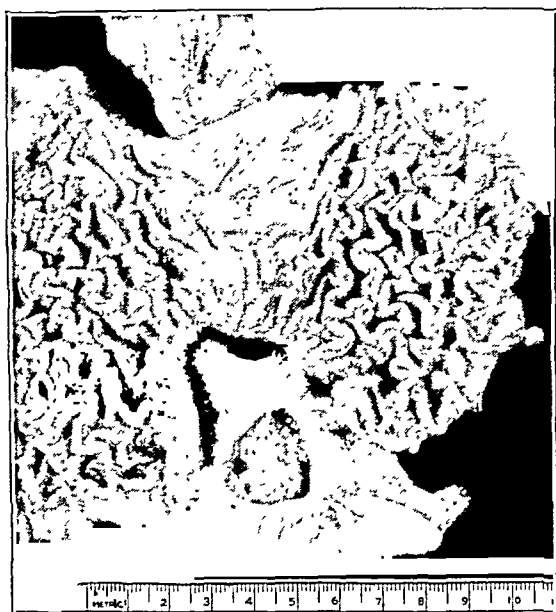


Fig. 3.—Gastrojejunal ulcer occurring in a dog on which the operation (antral excision) done on the patients in group 2 had been performed prior to the intramuscular injection of histamine in beeswax. Similar ulcers have been observed after the operation done on the patients in group 1 but not after the operation done on the patients in group 3.

SUMMARY AND CONCLUSIONS

Acid is the most important factor in the genesis of ulcer. By stimulating the intrinsic gastric secretory mechanism with histamine in beeswax, from which histamine is liberated slowly, ulcer may be produced in a large number of laboratory and domestic animals.

The most important criterion of an acceptable operation for ulcer is that it reduces gastric acidity effectually. On this basis of the eight types of operation subjected to scrutiny in this study, only two (operations 3 and 4A) appear to meet the requirements of a satis-

factory operation. The objectives of an acceptable operation are: (1) that it relieve the patient subjectively and remove the ulcer diathesis; (2) that it prevent recurrent ulcer; (3) that it do not compromise the future for the patient.

It appears that extensive removal of gastric tissue (three-quarter resection) is necessary to insure achlorhydria and to give assurance of meeting the first two requirements of an acceptable operation. Observation suggests that the achlorhydria of the three-quarter resection, so desirable to protect against recurrence of ulcer, meets adequately the third requirement of an acceptable operation, in that these patients lead active useful lives without evidence of any deficiency disorder.

The ulcer itself is not the item that should command the attention of the surgeon. It is the ulcer diathesis of the gastric secretory mechanism which demands his notice. The ulcer is merely the end effect of an overactive gastric secretion of acid. The only known manner in which the secretion of acid may be depressed effectually is by sacrificing a liberal portion of the gastric mucosa.

In order to insure achlorhydria, excision of the antral mucosa is mandatory. It is suggested that the antral mucosa may contain a hormonal stimulant of gastric secretion other than histamine.

SURGICAL TREATMENT OF DUODENAL ULCER

ARTHUR W. ALLEN, M.D.

Chief, East Surgical Service, Massachusetts General Hospital, and
Lecturer in Surgery, Harvard Medical School

BOSTON

Although it is now generally conceded that duodenal ulcer is a functional disorder and responds well to conservative measures, complications develop which require surgical intervention. Approximately 80 per cent of the patients with this lesion are taught to live in such a manner that they are comfortable and able to do their usual work. These persons may be successful in keeping completely symptom free if they refrain from worry and strain, eat properly and eliminate the use of tobacco, alcohol and condiments. Infringement of these rules may bring about recurrence or chronicity, which may well produce a situation that must be handled surgically. It is fair to say that a small percentage of these patients get into trouble in spite of rigid care. They are usually the victims of ulceration in an area that gives no warning of activation until massive hemorrhage or perforation takes place. Whether such a painless area exists in the duodenum of every human being is doubtful. There are, however, a considerable number of people who do have a silent area or whose lesion fails to produce the usual signs of activity, such as pain, heartburn and pylorospasm. Doubtless, the surgeon would see fewer patients in this group if the victim received the physical warnings that come to the average patient with ulcer. The index of discretion is well catalogued in the minds of the majority of such persons.

Less was known concerning the complex mechanism involved in the production of duodenal ulcer when operation directed toward relief of the condition became popular. Rest cures were not in vogue at that time. Hyperacidity was correctly believed to be the chief cause, but it took a long time to learn that there were other important contributory factors. If the early operations, conceived to produce a better neutralization of the gastric juice by the alkaline secretions of the liver and the pancreas, had been permanently successful and the operative mortality eliminated, it is doubtful if clinicians would ever have developed the understanding of the situation as it exists today. During this period of trial and error many types of operative procedures were devised. The immediate results of each new operation were excellent and were hopefully grasped as they were introduced; each advocate offered a good argument along

physiologic and mechanical lines. The terrible conditions which ultimately developed in so many of the victims of these procedures were indeed discouraging. So often a bad situation was turned into a frightful one, and no operation could ever be entirely without immediate risk. Under these circumstances, it is not difficult to understand how welcome has been the excellent progress of the internist, who has successfully developed a regimen that eliminates the need for operation in the majority of patients with duodenal ulcer. This leaves for surgical treatment approximately 20 per cent of these patients who come to a large urban general hospital. Acute perforation, massive hemorrhage, stenosis of the duodenum or the pylorus and intractability represent the complications of ulcer that are best treated by surgical methods.

ACUTE PERFORATION

Sudden perforation of duodenal ulcer is associated with a characteristic chain of symptoms and signs. Occasionally, the diagnosis is confused with renal colic in patients who have been liberal users of sodium bicarbonate, although the location and the radiation of pain and abdominal palpation should and usually do prevent error. Acute cholecystitis, acute appendicitis with perforation and acute pancreatitis also may be strongly considered in the differential diagnosis. As a matter of fact, the picture is usually clearcut, and even in the presence of difficulties of language one should have little trouble in arriving at the correct conclusion. Pain is severe and nearly always epigastric; collapse and shock of varying degrees are present. The pulse becomes elevated and the upper part of the abdomen rigid. Leukocytosis develops early. Roentgenograms of the abdomen taken with the patient in an upright position will show gas below the diaphragm in a large percentage of the cases.

The patient should be subjected to operation as soon as suitable conditions are available, since the earlier the perforation is closed the lower the mortality rate. Simple closure of the perforation is certainly the procedure of choice. This, I believe, is best done by Graham's¹ method of loosely fixing an omental tab over the perforation. This graft may be free or attached and is held in place by sutures passed above, below and through the ulcer site. Graham² reported only 2 deaths among 60 consecutive patients treated in this manner. This is the lowest published mortality rate that I have seen. Is the method of closure alone responsible for these excellent results? One must certainly give the method credit for its simplicity and rationale. This series did

1. Graham, R. R.: Perforated Ulcer, Surg., Gynec. & Obst. **64**:235-238, 1937.

2. Graham, R. R.: Technical Surgical Procedures for Gastric and Duodenal Ulcer, Surg., Gynec. & Obst. **66**:269-287, 1938.

not include only cases in which the risks were good and the perforations were recognized early. Doubtless, a coordinated effort in preoperative treatment and postoperative care played a large role in the successful outcome in this group of cases.

The choice of anesthesia is important. This is a poor operation with which to use inhalation anesthesia unless suction is maintained on a previously introduced Levine tube. At all costs, one must prevent inhalation of the stomach contents during operation. Although many of the patients do not vomit, some are apt to do so as soon as administration of the anesthetic is started, particularly if the anesthetic is of the inhalation variety. The tube should be introduced into the stomach before operation and kept there for several days afterward, regardless of the type of anesthesia used. Spinal and local anesthetics have their champions, and between them there is little choice, provided each is used correctly.

Care should be used to aspirate the fluid from the abdominal cavity. It is particularly useful to remove the collection from above the liver, for this diminishes the chance of subdiaphragmatic abscess. If there has been much delay in operation or there is an abnormal amount of extravasation of the contents of the stomach and the duodenum, it may be well to remove this material from the pelvis. This is best done by making a suprapubic stab wound, and then while the intestines are protected by the left hand from the upper wound, the suction tip can be introduced into the pelvis through the lower. If one is tempted to drain the abdomen under these circumstances, the wicks through the lower wound into the pelvis should be removed within forty-eight hours. The danger of obstruction of the small bowel is more serious than that of the development of a pelvic abscess. One must be careful not to introduce a drainage tube or wick to the site of the perforation since it is almost sure to produce a duodenal fistula. If one feels it necessary to drain the region, such drainage should be established in the subhepatic pouch of Morrison. The introduction of sulfanilamide powder into the abdomen after this and other operations on the duodenum is becoming popular. It will take some time to interpret the results of this use of the drug, but one must not rely on it as a substitute for good technic and after-care.

Closure of the perforation by suture has been the usual procedure. When one sees the wide extension of the induration about such an ulcer, it seems incredible that suture has met with its usual success. I feel that one of two things often happens—either the sutures infold so much of the area that obstruction takes place or they gradually give way while nature closes the opening by secondary adhesions to neighboring structures. Excision of the ulcer with closure of normal tissue has

been recommended by some operators. This I know to be unnecessary, and it does not meet with any better results than more simple procedures. Others have advocated a radical subtotal gastrectomy at this time. I believe that this operation, as well as concomitant gastroenterostomy or pyloroplasty, is unwarranted for this type of extremely ill patient. Any procedure should be looked on as a life-saving measure.

There is some evidence that one might consider conservative measures only in the treatment of acute perforated ulcer. This is based on the facts that Wangenstein suction, intravenous feedings and other measures will enhance healing of the ulcer and that peritoneal contamination will be cared for under a regimen of physiologic gastrointestinal rest. I have had slight experience with this type of treatment, but I feel that one can more safely carry out these measures after the leak has been stopped. It will take much courage and some years of experience to be able to show that the results with these conservative methods alone are comparable to those with the combination of closure and logical after-care.

That patients who have survived closure of a perforated ulcer should have at a time of election a radical procedure I may in time advocate, although my present studies do not warrant making this a blanket recommendation.

CICATRICAL STENOSIS

During the healing process associated with repeated recurrence or the prolonged activity of duodenal ulcer, scar tissue may be formed in such a fashion as eventually to obstruct the outlet of the stomach. This occurs usually after the age of 60 and often after a considerable respite from acute symptoms. The onset is apt to be gradual, and the patient may enter the hospital with marked chronic dilatation of the stomach. In such cases, acidity is likely to be normal or even low. This low acid level in the opinion of Ochsner, Gage and Hosoi³ is due to the effect of prolonged gastritis on the acid cells. Such patients must be accepted for operation, or starvation will take place.

It has been generally agreed by surgeons of experience in this field that this is the one remaining situation created by duodenal ulcer that warrants a palliative short circuit type of operation. Certainly, the prompt relief afforded by pyloroplasty, gastroduodenostomy, or gastroenterostomy is convincing. I⁴ have advocated posterior gastroenterostomy for use in this situation as being the simplest and safest procedure

3. Ochsner, A.; Gage, M., and Hosoi, K.: Treatment of Peptic Ulcer Based on Physiological Principles, Surg., Gynec. & Obst. **62**:257-274, 1936.

4. Allen, A. W., and Welch, C. E.: The Role of Surgery in Peptic Ulcer, South. M. J. **31**:418-425, 1938; Peptic Ulcer Considered from a Surgical Point of View, New England J. Med. **220**:103-106, 1939.

I had used. I have now come to look on this operation, even for this type of patient, with some misgiving. In at least 2 men in late life, who had brilliant relief of disability after posterior gastroenterostomy which I did for cicatricial obstruction, jejunal ulcers have developed. One, past 80 years of age, bled acutely and alarmingly from his stomal ulcer. Each of these catastrophies followed the death of the patient's wife, after which the usual restrictions on the use of alcohol and tobacco were abandoned. It is my belief that restoration of function of the stomach allows a return of the usual acid activity and thus brings about the earlier vulnerability of such persons. It illustrates well the old dictum that "once an ulcer patient, always an ulcer patient," and the patient cannot break training even after cure by the physiologic changes of old age and the temporary reduction of acid by gastritis.

In patients in this group who present good risks, I am inclined to attempt a slow careful preparation. This includes Wangenstein suction for a few days and then physiologic rest of the stomach as described by Peters,⁵ who has brought to attention the fact that the secretions of the salivary and the stomach glands will pass through an almost completely obstructed pylorus provided the stimulation of extra secretions by water and food or an inlying tube are withheld. Performing jejunostomy for feeding in such a patient will make it possible to delay operation until a proper chemical and fluid balance will permit a more radical operation. In treating the less elderly patients of this group, i. e., those between 50 and 70, I feel that serious consideration should be given to the possibility of subtotal gastrectomy rather than gastroenterostomy. This should be particularly thought of in treating the person who has found it difficult to live with his ulcer prior to the time of obstruction by scar tissue. Whether one decides on conservative posterior gastroenterostomy or a more radical operation, it is wise to decompress the stomach a few days before surgical intervention is undertaken. If gastroenterostomy is done, a slightly longer loop should be used, since the stomach will contract after the short circuit is made, and a poor stoma may result.

One should be careful not to confuse the group of patients just discussed with those with edematous obstruction frequently seen with reactivity of duodenal ulcer. These patients come into the hospital with complete obstruction, to be sure, but they are easily differentiated from those of the other group. As a rule they are younger and have a history of rapid recurrence of symptoms. Such patients after treatment by continuous suction for a few days followed by complete elimination of secretory stimulation will be able to take a thin diet in a week or ten

5. Peters, J. P.: The Structure of the Blood in Relation to Surgical Problems, *Tr. Am. S. A.* **58**:8-16, 1940.

days. These patients will soon reach a quiescent stage and on a careful regimen may even carry on indefinitely. I once felt that it was best to advise radical operation for patients in this group at a time of election. One should wait until the ulcer is well healed before undertaking a surgical procedure since the induration spreads to surrounding structures to an alarming degree. If one operates too early, it may be necessary to plan a two stage procedure or accept an unwarranted hazard with the duodenal stump. It often happens that by the time such a patient is judged ready for a radical procedure, he is symptomatically and objectively well. Under such circumstances, it is easy to be persuaded to allow the continuation of, or the establishment of, a sound conservative regimen.

MASSIVE BLEEDING

Approximately one third of all patients admitted to the wards of the Massachusetts General Hospital with duodenal ulcer have had gross bleeding. Of these, 36 per cent had sufficient loss of blood to produce severe anemia. Two thirds of those in the group with severe bleeding bled acutely in massive amounts. Actually, there were 94 such patients in the decade from 1923 to 1932,⁶ a period during which 1,002 patients with duodenal ulcer were admitted to the wards. Of these 94 patients with acute hemorrhage, 13 bled to death. In a check of the situation from 1933 to 1941 in the same institution I found there had been 80 patients with acute severe hemorrhage, 9 of whom died. Thus, more modern management appears to have little effect on the mortality rate in this clinic.

In a study of this situation for the twenty year period prior to 1933, Benedict and I analyzed all the factors contributory to fatal massive hemorrhage from duodenal ulcer in 138 patients admitted to the hospital during that period.⁷ We found, much to our surprise, that chronicity, repeated episodes of bleeding and most of the concomitant diseases had little relation to the fatalities. We expected that the patients with chronic, callous ulcers of long standing would be the type that would not spontaneously recover. The duration of symptoms in the recovered group was seven and seven-tenths years as against eight and one-tenth years for the group in which the patients succumbed to hemorrhage; this is not enough difference to approach even nearly the discrepancy in the age groups of those who recovered or died. The factor of repeated episodes of bleeding, which we thought would throw light on the subject, also was surprising; we found that in 9 of 20 cases in which

6. Allen, A. W.: Acute Massive Hemorrhage from the Upper Gastrointestinal Tract, *Surgery* 2:713-731, 1937.

7. Allen, A. W., and Benedict, E. B.: Acute Massive Hemorrhage from Duodenal Ulcer, *Ann. Surg.* 98:736-748, 1933.

death occurred, there had been no bleeding previous to the final admission. Ten patients had bled only once before, and 1 patient was admitted for his fifth episode of bleeding. Five of the patients who died had used alcohol to excess.

The Age Factor.—The age difference between the patients who recovered spontaneously and those who died was really the most striking finding in this study. The average age of those who died was 56.3 years as against 41.8 years for those who recovered. Actually, there were 2 deaths of patients under 49 years of age. The other 18 fatalities were of patients of or beyond this age. There were more than twice as many patients in the younger as in the older age group. In the past eight years (Jan. 1, 1933 to Jan. 1, 1941), only 1 patient of the 9 who died was under 50 years of age, and he was 44. In the spring of 1941, a man of 30 did succumb to massive hemorrhage from duodenal ulcer. I believe that I am justified in making some definite conclusions from these data. Certainly, those patients with enough arteriosclerosis to interfere with adequate thrombus formation in the bleeding vessel should be considered in a different category from those in the younger age group. Actually, in my experience the chance of the spontaneous recovery of those under the age of 45 was about 95 per cent, while for those beyond the age of 50 the chance was reduced to about 70 per cent.

Therefore, I believe that the younger patients should be treated conservatively until they have made a complete recovery; after this I advise a radical operation. This opinion is based on the fact that many of the patients who bleed severely get little warning of activity before sudden loss of blood takes place; moreover, their ulcers penetrate deeply and frequently are difficult to keep pain free. One should change the term "advise operation" to "urge operation" for patients beyond the age of 45 who have recovered spontaneously from severe massive hemorrhage. This policy should be extended to those who bleed without warning of renewed activity and to those whose hemorrhage occurs while they are submitting to a logical ulcer regimen, regardless of age.

Each patient beyond 45 years of age should be immediately hospitalized and his condition carefully evaluated. If there is doubt concerning the source of the bleeding, a fluoroscopic examination should be made as soon as the patient has recovered from shock. This requires the ingestion of only a small amount of barium sulfate, and with Hampton's⁸ technic the crater can be easily visualized without palpation. I have seen no harm from any examination of this type made during the active phase of hemorrhage. Actually, these victims bleed intermittently, as can be determined from the pulse rate and the blood pressure charts; each new

8. Hampton, A. O.: A Safe Method for the Roentgenological Demonstration of Bleeding Duodenal Ulcer, *Am. J. Roentgenol.* **38**:565-570, 1937.

burst of bleeding causes the typical signs of shock. There are a variety of factors that enter into such a picture, and one may feel that a certain patient—judging from his robust appearance and the softness of his peripheral vessels—will spontaneously cease to bleed. As a matter of fact, many patients have only one severe hemorrhage and no subsequent bleeding during the episode. Others will have bursts at intervals of four to twenty-four hours, either prior to admission or while under observation. If these patients are somewhat arteriosclerotic but otherwise present good risks, there is no reason to permit them to succumb to hemorrhage. The decision for or against operation must be made early, and that means within seventy-two hours after onset. If operation is undertaken before the effects of starvation are present, the outcome will be successful. If one postpones surgical intervention until it is obvious that the patient will die of hemorrhage, the chance of success is small. Having made the decision to try conservative treatment, one should not, after a week or more of intermittent bleeding to repeated shock levels, be persuaded to attempt operation. Such a patient will survive the procedure nicely only to succumb to infection or pneumonia a few days later. I have proved that this is true of the older patients. It might be possible to rescue such a patient if the absence of food absorption could be counteracted or to save a young patient who might be expected to recover spontaneously.

Should operation be decided on in the early days of acute massive hemorrhage, one must approach the problem in a logical manner. As soon as the bleeding vessels are ligated, the patient should be supported by sufficient blood to replace his loss. The anesthesia should be spinal or local, since inhalation anesthesia is even more dangerous to a person in this depleted state than to the average person of his age. The operation should be planned to interrupt the three tributaries to the gastroduodenal artery lying behind the duodenum and transversing the head of the pancreas. This, I believe, is best done by transecting the stomach and approaching the vessels from the under side of the pyloric region as previously described. I have successfully accomplished this in 5 patients with duodenal ulcer and 3 with gastric ulcer who experienced acute massive bleeding and were operated on in the early days after onset. All of these patients were over 50 years of age. I have recently failed in operating on an elderly man; he had been bleeding ten days, and I should not have been tempted to operate on him. He died of bronchopneumonia on the sixth postoperative day. Another failure occurred in the case of a man of 60 owing to perforation of the ulcer three days after modified subtotal resection for exclusion. I successfully stopped the hemorrhage but made the mistake of freeing the lower segment of the duodenum before determining that the ulceration extended from

the pylorus to the bile ducts. The antrum was then transected and its mucosa removed. At autopsy, all suture lines were tight, but the huge 2 cm. ulcer had perforated into the free abdominal cavity. This patient had been successfully brought through resection of a gastrojejunal fistula two years before and had been urged to submit to subtotal gastrectomy one year prior to his last admission during a phase of activity of the original duodenal ulcer. In retrospect I see that I should have been able to determine by the extent of the inflammatory reaction that resection beyond this huge ulcer would be hazardous and that I should have contented myself with the resection as carried out without disturbing the adhesive protection about the ulcer site. It further bears out the fact that radical gastrectomy should be performed on patients with gastrojejunal fistula as a final stage of their treatment, for protection against recurrence of the original duodenal ulcer.

I am not in accord with the principles set down by some of my colleagues regarding early operation for acute massive hemorrhage in patients of all age groups. I admit that the younger patients are more likely to survive radical procedures than the older ones; likewise, I agree that these patients can be saved a good deal of time by immediate operation. On the other hand, I feel that with a large number of such operations one must expect a mortality rate of over 5 per cent, a figure that is too high for subtotal gastrectomy of election. Furthermore, it can be expected that at least 95 per cent of the younger patients coming to the hospital will cease to bleed spontaneously. It is fair to say that the time lost to the patient in getting into proper condition for a radical operation plus the small chance that bleeding will continue plus the ultimate operative mortality during a quiescent period all add up to a tempting argument.

There is a group of patients with duodenal ulcer who do not bleed acutely in massive amounts but whose blood loss is gradual and sufficient in quantity to cause marked anemia. These persons do not have a large open vessel but bleed from numerous smaller ones in and about the ulcer site. This type of bleeding is often associated with some pyloric obstruction. Occasionally, such a patient will require surgical intervention in order that proper feeding can be carried out. Under these circumstances, the patient is often in such a depleted state that some two stage operation is indicated. Most of the patients in this group will respond to a careful hospital regimen and finally cease to bleed and regain a normal state of health. Rarely, however, does a patient of this type remain symptom free. For this reason the patient should, at a time of election if possible, be subjected to radical subtotal resection.

INTRACTABILITY

Duodenal ulcer is intractable in a variety of cases. These cases represent approximately only 5 per cent of all cases of duodenal ulcer. They are difficult to define since so many factors enter the picture.

The location of the ulcer probably accounts for the intractability in the majority of the cases. Three sites are of importance: 1. When the ulceration is close to or actually involves the pylorus itself, there occurs a condition not unlike an anal fissure. As the pylorus opens and closes, there is a tendency to slow healing, and frequently the respites of comfort are of short duration. 2. An ulcer that penetrates deeply into the pancreas may not erode a large vessel as ulcers often do, but such a deep erosion is prone to heal slowly or recur frequently. The pain referred through to the back is often characteristic of such a lesion. 3. Graham² has described a "duodenal ulcer occulta" located on the posterior wall of the descending limb of the duodenum. An ulcer in this area is difficult to show in a roentgenogram and sometimes involves the biliary ducts. Often it is associated with a high transverse stomach in a moderately fat barrel-chested person. Accurate diagnosis may demand surgical exploration. I have seen patients with such ulcers living on a careful regimen and unable to become symptom free. The absence of roentgen confirmation is often disturbing, and an attempt may be made to explain the situation on the basis of a small hiatal hernia or disease of the biliary tract.

Economic factors often make it difficult to keep a patient with an ulcer free of discomfort. If a man has a family to support or has any self respect, he must keep at his job. It is easy enough to say that he must change his occupation if it is incompatible with the proper ulcer regimen. That this is impracticable in many instances is obvious. I have known such patients to carry rations of suitable food with them to work and try in every reasonable way to keep their ulcer symptoms under control, only to find that they could not. At rest, particularly in the hospital ward, they are fine, and all goes well, but almost as soon as they return to work, the symptoms reappear. The type I am referring to now is not the high pressure person who has too much nervous tension to work and keep his ulcer under control. The ordinary moderately calm worker at a simple job may have to take the attitude that if no cure can be offered, he must either devote his time to taking care of himself or disregard the consequences of his ulcer and continue his work as best he can.

Psychologic factors should be carefully taken into consideration. Often advice from this viewpoint will turn the tide and make it possible for some persons to master their ulcer situation and continue to be an economic unit of society. Certainly, the physician should not overlook

this possibility before accepting an ulcer as intractable to conservative measures. I can recall one suicide that might have been prevented if the psychologic factors had been properly evaluated.

Intellectual stamina is perhaps a vague term, but the lack of it in some patients with ulcer keeps all concerned unhappy. In this group is the patient who will not give up alcohol and tobacco. He will cheat on the type of food best for him and will drive himself at play or in business to an extent incompatible with an ulcer diathesis. Admittedly, some persons of this type are of sufficiently low intelligence by birth that they are not to be held entirely accountable. Under these circumstances the surgeon may with a clear conscience attempt to achieve a better physiologic and mechanical setup for the patient.

I am not so sanguine, however, about accepting for a hazardous operation a patient who knows his faults but will not correct them. I am not surprised that some of my medical colleagues feel that they cannot carry the distasteful problem of coddling such a patient to an extreme. The surgeon, on the other hand, does not look with any pleasure on accepting such a patient, since he knows that after operation there will be no help from the patient himself. The whole challenge is to the operation alone, which all realize has not been perfected to such a foolproof degree that cooperation from the patient is not essential.

OPERATIVE PROCEDURES

With the possible exception of cicatricial obstruction in aged patients, there is a definite consensus at the present time that operation for cure of duodenal ulcer means radical subtotal gastrectomy. This has come about through a long period of trial and error, during which every conceivable procedure of a less radical nature has been attempted. It is apparent now that one must remove a large proportion of the acid cells in the fundus as well as the acid-activating cells of the antrum to lower continuously the acid level in the remaining stomach segment. This has resulted in a higher percentage of patients with long respites from further ulceration than any of the more conservative operations. Strangely enough, as experience has been gained in this field, the mortality rate for the radical operation appears to be actually lower than the rates for many of the lesser procedures. Doubtless, this statement is open to criticism, since it is apparent that present day gastric surgical procedure is attended by a better understanding of the numerous factors of safety, an understanding that has come about through many channels.

In the minds of those interested in the subject, subtotal gastrectomy means the actual removal of not less than two thirds of the stomach. Wangenstein and associates⁹ made some interesting measurements of

9. Wangenstein, O. H.; Varco, R. L.; Hay, L.; Walpole, S., and Trach, B.: Gastric Acidity Before and After Operative Procedure with Special Reference to the Role of the Pylorus and Antrum, *Ann. Surg.* **112**:626-667, 1940.

the actual square centimeters that constitute a subtotal resection. Various men have used the terms "more than one half," "two thirds," "three fourths" and "four fifths" of the stomach volume to indicate what is meant by adequate resection. There have been advocates of the shoe-maker type of resection on the basis that the antrum and the lesser curvature were the important structures to eliminate. Others have felt that the lesser curvature was not important to remove but that the fundus should be almost completely eliminated.¹⁰ Provided one removes sufficient of the acid glands and all of the acid-activating hormone area, one may have some leeway in the actual maneuver. There is considerable experimental and clinical evidence to indicate that removal of the greater part of the lesser curvature and as much of the fundus as can be removed with comfort leaves a situation less likely to be followed by subsequent ulceration.

Finsterer's¹¹ idea of leaving enough of the antrum for easy closure and proceeding with subtotal gastrectomy proximal to this region in order to avoid the difficult mobilization of the duodenum in certain cases of extensive ulceration has met with too much favor. This he called resection for exclusion and apparently indicated that removal of the antral mucosa was worth while, although this step in the procedure has often been overlooked.

Ogilvie¹² described a similar operation based on physiologic principles and recommended the preservation of the antrum in order to prevent anemia after partial gastrectomy. He¹³ emphatically retracted his belief in this operation and reported nine jejunal ulcers in 22 patients on whom he had performed physiologic gastrectomy. I performed this operation on 5 patients with duodenal ulcer and 3 with gastric ulcer and have abandoned it because in 4 of the patients with duodenal ulcer and in 1 with gastric ulcer jejunal ulcer developed. In a fair number of cases I have practiced removal of the antral mucosa as suggested by Bancroft¹⁴ when it seemed impracticable to resect beyond the ulcer site in the duodenum. It would appear that the results in this group of cases are going to be as good as those in cases in which complete

10. Connell, F. G.: Fundusectomy: A New Principle in the Treatment of Gastric or Duodenal Ulcer, *Surg., Gynec. & Obst.* **49**:696-701, 1929. Zollinger, R.: Gastric Resection with Removal of the Fundus in the Treatment of Duodenal Ulcer, *Surgery* **8**:79-93, 1940.

11. Finsterer, H., and Cunha, F.: The Surgical Treatment of Duodenal Ulcer, *Surg., Gynec. & Obst.* **52**:1099-1114, 1931.

12. Ogilvie, W. H.: Physiology and the Surgeon, *Edinburgh M. J.* **43**:61-83, 1936.

13. Ogilvie, W. H.: The Approach to Gastric Surgery, *Lancet* **2**:235 and 295, 1938.

14. Bancroft, F. W.: Modification of Devine Operation for Pyloric Exclusion of Duodenal Ulcer, *Am. J. Surg.* **16**:223-230, 1932.

subtotal resection was done. I am aware that great care must be used in denuding the antrum of its mucosa; if care is not exercised, perforation of the thinned-out muscularis and serosa will take place. This remnant is also a delicate structure to invert, and care must be used to make an adequate closure. I have often been tempted to try Schrimmer's¹⁵ idea of suturing the two denuded surfaces together without infolding, but as yet I have not used it.

It is admitted that one can, with greater comfort, turn in an adequate segment of antrum that has not been denuded and also that morbidity is higher among those patients having either difficult closure of the duodenal stump or closure of a denuded antrum. McKittrick¹⁶ therefore felt that it might be wiser to accept a two stage procedure and do resection for exclusion as a first stage. Six weeks later, after complete subsidence of all inflammatory reaction, an easy resection of the pyloric segment can be accomplished. I am convinced that for use in selected cases this idea has much to commend it. I have been impressed with the ease of removal of such a segment after the occurrence of jejunal ulcer following the von Eiselsberg¹⁷ or the Devine¹⁸ operation or Finsterer's resection for exclusion.

I have usually employed a left rectus muscle retraction incision. As a rule, this gives adequate exposure of the upper segment of the stomach and allows for easy anastomosis. However, it does handicap somewhat the proper management of the duodenal stump in some cases. When the stomach is high and in a transverse position or when the patient has a wide flare of the costal border, I prefer either an oblique or some other modification of a transverse incision. I begin by selecting a site on the greater curvature well to the left of the junction of the right and left gastroepiploic vessels. The radicals of these vessels supplying the fundus are interrupted along the greater curvature, thus preserving the main vessels and the blood supply to the great omentum. This first maneuver is carried down to the antrum. Then the vessels of the lesser curvature are secured as far proximal as is practical. The stomach is then divided between heavy crushing clamps and the distal segment is lifted up, exposing the attachments of the antrum to the pancreas and the middle colic vessels. The remaining dissection depends on the acuteness and the inflammatory extension of the ulcer. If the area

15. Schrimmer, F. A. C.: A Technic for the Management of Gastrojejunal Ulcers With or Without Gastro Colic or Jejuno Colic Fistula, *Ann. Surg.* **104**: 594-600, 1936.

16. McKittrick, L. S.: Personal communications to the author.

17. von Eiselsberg, A.: Ueber Ausschaltung inoperabler Pylorusstricturen nebst Bemerkungen über die Jejunostomie, *Arch. f. klin. Chir.* **50**:919-939, 1895.

18. Devine, H. B.: Basic Principles and Supreme Difficulties in Gastric Surgery, *Surg., Gynec. & Obst.* **40**:1-16, 1925.

involved obviously extends to the region of the bile ducts and the great vessels to the liver, a modified exclusion operation is done. I have denuded this remaining distal segment of its mucosa, hoping that this would eliminate anastomotic ulcer. If one prefers to leave the antral mucosa under these circumstances, then a second operation at a later date must be planned to eliminate this segment. I have abandoned the policy of cutting across the duodenum at the upper border of an ulcer on the posterior wall and leaving the ulcer bed attached. Although one can get fair closure by suturing the anterior wall of the duodenum to the pancreas, in such cases there has been more trouble with leakage and abscess formation. I am convinced that if the duodenum is transected, this should be done in such a manner that at least 2 cm. of free bowel remains for an adequate turn in. This is possible with all quiescent ulcers, and most of these are sufficiently high to allow resection of the ulcer site, even if they are on the posterior wall. If the ulcer is on the descending limb of the duodenum, one can often find sufficient free intestine proximal to the ulcer but distal to the pyloric sphincter to make a satisfactory closure. I am convinced that actual removal of the ulcer itself is unimportant. Much help can be obtained by freeing the duodenum from its outer attachments as first described by Finney.¹⁹ This exposes the course of the common bile duct so that one can easily determine the entry of the duct into the duodenum. Many adherent ulcers can be included in the resection if this precaution is carried out which on first inspection appears to be too extensive to permit mobilization and closure of the stump. The only risk one must accept in such a maneuver is that having freed the ulcer site too extensively to allow leaving it, one finds that actually it is too close to the papilla of Vater to allow adequate closure. This may be avoided in two ways. One way is not to disturb the ulcer itself but to use the modified exclusion procedure I have advised or accept a two stage operation. If, on the other hand, one only frees the outer attachments of the duodenum and looks over the situation, no harm results, and in many cases the ulcer is found to be well above the papilla of Vater.

Types of anastomosis between the stomach segment and the jejunum are varied; they are all modifications of the Billroth II idea. Some prefer closing the upper half or two thirds of the cut end of the stomach as suggested by Hofmeister²⁰ and utilizing the fundal segment for anastomosis. Finsterer expressed the opinion that by attaching the unopened proximal segment of the jejunum to the upper, turned-in portion of the stomach a better mechanical and physiologic stoma is

• 19. Finney, J. M. T.: A New Method of Pyloroplasty, *Tr. Am. S. A.* **20**:165, 1902.

20 Hofmeister, F., cited by Stumpf, R.: *Beitrag zur Magen Chirurgie*, *Beitr. z. klin. Chir.* **59**:551, 1908.

produced. Graham, using a shoemaker clamp on the upper segment, obtained the same result but left more of the fundus than some believe to be safe. May²¹ recently advocated a form of anastomosis that utilizes the entire cut surface of the stomach, but by puckering the stomach edge the resulting stoma is centrally placed and the lower margin elevated to prevent dumping. I have often been able to use the entire segment of the stomach by drawing the freed organ strongly toward the right; the structure is thus made tubelike before the clamps are applied. After anastomosis, when this is done, the stoma assumes an oblique or nearly transverse direction, which has given satisfactory results. I have seen no disabling symptoms from rapid emptying. If the stomach is large, I usually close the lesser curvature portion and utilize the fundal half in the anastomosis. By starting each row of sutures at the lesser curvature segment, one above the other, I accomplish much the same mechanical situation that Finsterer has advocated. I use two rows of fine chromicized catgut on atraumatic needles without silk reenforcement. Postoperative hemorrhage and leakage have not occurred in my cases.

There is considerable controversy regarding antecolic and retrocolic anastomosis. Lahey,²² Rienhoff,²³ McClure²⁴ and others have preferred to use the antecolic route as a rule. They have found it easier to carry out; they have reported little trouble from the long proximal loop regurgitating large quantities of bile into the stomach when the patient lies down, and they like its accessibility if reoperation should become necessary. I have tested many patients with the idea of performing anterior anastomosis, only to find that often the jejunal mesentery was not long enough to permit an anterior hook-up to the high short stomach segment without tension. Actually, on some occasions when I felt it important to make an antecolic anastomosis, I have divided a heavy great omentum from its distal border to the colon in order to carry out the procedure. Occasionally, I have seen disturbing partial obstruction to the colon during the convalescence due, I believe, to the pressure of the jejunum on the large bowel while adjustments were taking place. One should never be tempted to use enteroenterostomy between the long loops of the jejunum when dealing with ulcer, although this will often simplify

21. May, H.: Reconstruction of the Stomach Outlet in Gastric Resection: Simple Suture for Use with the Billroth 2 Oral Totalis Type of Operation, *Arch. Surg.* **44**:378 (Feb.) 1942.

22. Lahey, F. H., and Marshall, S. F.: Surgical Treatment of Peptic Ulcer Based upon One Hundred and Thirty Subtotal Gastrectomies for Peptic Ulcer, *New England J. Med.* **217**:933-940 (Dec. 9) 1937

23. Rienhoff, W. F., Jr.: Sympathetic Nerve Block as an Adjunct Anesthesia in Minimal Resection of the Stomach for Peptic Ulcer, *Ann. Surg.* **110**:886-906, 1939.

24. McClure, R. D., and Fallis, L. S.: Partial Gastrectomy: A Consideration of Certain Technical Problems, *Ann. Surg.* **111**:743-758, 1940.

the convalescence after high resection for cancer. In the presence of acid, jejunal ulcer will follow enteroenterostomy in a high percentage of cases. Walters, Lewis and Lemon²⁵ emphasized this hazard in a recent publication and used this as an argument against antecolic anastomosis.

I prefer a short loop retrocolic anastomosis in the average virgin case of ulcer in which the patient has a thin mesocolon. I am careful to suture the rent in the mesocolon to the stomach segment above the anastomosis; the posterior row of these sutures is placed before the anastomosis is done. It is important to make the opening in the mesentery to the left of the mesenteric vessels, since if this detail is overlooked malfunction is more apt to occur. In a patient who has had a previous operation on the stomach, particularly posterior gastroenterostomy, I feel it unwise to place the new stoma through the traumatized mesocolon. Likewise, in a patient with a thick fatty mesentery and one with a short mesocolon, I prefer the antecolic route. The tendency for the small bowel to attach itself to traumatized fat causes many complications. When peritonealization of the mesentery or its edge cannot be carried out, the anastomosis should be made as far away from such an area as possible.

After-Care.—The after-care of patients subjected to this type of operation is most important. I leave a previously introduced Levine tube in the stomach until a satisfactory gastric balance is assured. Feedings are gradually increased, and great care is used not to force food by mouth. If the patient is hungry, his feedings will nearly always pass through the stoma. If he eats when he feels full or does not desire it, dilation of the stomach segment will take place and delay convalescence. In the patient on the borderline of starvation one may use the Abbott-Rawson tube; this keeps the stomach segment empty but allows feeding directly into the distal jejunal limb. In many cases I have provided concomitant jejunostomy for feeding. This is particularly important when the serum protein has had to be brought to operable levels by blood transfusion. Clute²⁶ recommended an almost routine use of concomitant jejunostomy. If all goes well, the average patient can take a maintenance diet by the third postoperative day. He may be out of bed by the twelfth day and be able to go home on the eighteenth. He is usually able to resume his ordinary occupation by the end of the third month. He should remain under observation and be advised to continue to observe a reasonable regimen indefinitely. I have been

25. Walters, W.; Lewis, E., and Lemon, R.: Primary Partial Gastrectomy (Polya Type) for Duodenal Ulcer: A Study of Results in Two Hundred and Twelve Cases, *Surg., Gynec. & Obst.* **71**:240-243 (Aug.) 1940.

26. Clute, H. M., and Bett, L. M.: Jejunostomy for Postoperative Feeding, *Tr. South. S. A.* **53**:295-307, 1940.

impressed by the freedom from symptoms, by the fact that the usual three meals a day are satisfying, and by the ability of patients of this type to carry their regular economic load.

COMPLICATIONS

After subtotal gastrectomy for duodenal ulcer, I have had two chief reasons to worry. One is that an improperly handled duodenal stump may cause fistula, abscess, peritonitis or subdiaphragmatic infection. Though it happens only rarely that a duodenal stump is improperly handled, it is of sufficient importance to warrant careful management of this part of the operation. I have already pointed out many of the pitfalls, but I reiterate that if adequate closure of free uninvolved duodenum cannot be done, then a modification of the exclusion idea should be used.

The other complication is that of malfunction of the stoma. This, to be sure, occurs infrequently, but when it does, it calls for proper management. Some anastomoses fail to work from the beginning, and others function well for a number of days and then become occluded. Doubtless there are several factors at work, although poor mechanics, infection with resulting adhesions and edema from hypoproteinemia cover most of them. I have seen so many patients spontaneously recover from obstruction that I believe the obstruction in such cases is on the basis of either temporary edema at the suture line or inadvertent, insidious acute dilatation of the proximal stomach segment. Both factors may well have played a role. On the basis that the complication may be temporary, one should keep the stomach decompressed and treat the patient expectantly for at least a week. Welch and I²⁷ have shown that in treating young patients it is safe to delay intervention for a longer interval than in treating the older patients. I have further demonstrated to my own satisfaction that if the mechanical procedure is correctly carried out at the original operation, one need not interfere with the anastomosis. Jejunostomy for feeding, if done in time, will invariably allow nature to correct the faults at work about the stoma. This may take as long as fifty days and test the endurance of the victim and the surgeon to the utmost. The only exception to this rule that I have encountered was in the case of a patient who had posterior anastomosis made to the right of the mesenteric vessels through a short mesocolon. This patient eventually required revision of the anastomosis before relief was complete.

Although there has been a good deal of worry in the past as to hemorrhage at the suture line, this has not been a frequent occurrence in recent years. I believe that the use of crushing clamps on the

²⁷ Allen, A. W., and Welch, C. E.: Jejunostomy for the Relief of Malfunctioning Gastro-Enterostomy Stoma, *Surgery* 9:163-182, 1941.

remaining stomach segment helps to eliminate bleeding. Also, one must use considerable care to secure and ligate separately active vessels during anastomosis. The care with which tension is maintained on the suture and the manner in which the sutures are introduced do much to eliminate this complication.

Leakage of a suture line is in the same category as hemorrhage. One rarely hears of it now, but precautionary measures are always to be taken into consideration. The usual rules of good gastrointestinal surgical procedure apply. One must approximate without tension the two serous surfaces of the structures to be anastomosed. It is important to turn the mucosal edges into the open viscus. I believe that this is best accomplished by an inside and an outside row of sutures, the former inverting the mucosa. I think it unwise to use a third row of catgut sutures since this is simply a foreign body which nature must absorb, and it thus offsets any good that may come from it. I have found no fault with two rows of continuous fine chromicized catgut—the size 0 or 00 being adequate, depending on the make. I have not found a row of interrupted silk to be of any advantage.

Infection is, to be sure, always uppermost in the mind. Some duodenal ulcers harbor a virulent organism, and in 2 cases in my experience this has proved disastrous. At the moment I feel that care in walling off the field of operation, the use of suction on the inlying Levine tube and the employment of a suction tip during operation constitute the most satisfactory safeguards. I have had too little experience with the preoperative use of sulfaguanidine (sulfanilylguanidine) to warrant any opinion as to its efficacy. Cultures taken at operation after its use have so far not been convincing as to its value. The use of sulfanilamide powder in and about the operative field may prove of great aid in eliminating uncontrollable infection, but much more experience is needed to evaluate this procedure completely. I admit that I use it in all cases in which gastrectomy is done for malignant disease and in many cases in which resection is performed for ulcer. Wangensteen²⁸ devised a clamp suitable for aseptic anastomosis between the jejunum and the stomach. The method will certainly have strong supporters for its use in gastric resection for infected lesions, particularly cancer.

Pulmonary complications of varying degrees following gastric operations are still a problem. I am inclined to believe that some of the efficacy of procaine hydrochloride in inducing anesthesia and splanchnic block is due to the effect of this anesthetic on the vagus nerves. Adams²⁹

28. Wangensteen, O. H.: *Aseptic Gastric Resection*, Surg., Gynec. & Obst. **70**:59-70, 1940.

29. Adams, R.: Personal communications to the author.

called my attention to the importance of procaine hydrochloride block of the vagus nerves during operations on the lung. He expressed the opinion that the same principles apply to gastric operations and that if the vagi are well anesthetized before sectioning, there will be a marked diminution in postoperative atelectasis. Pneumonia is far less dangerous than before the days of sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine). There are patients in a depleted condition, however, who cannot withstand pneumonia and surgical trauma combined, even with use of the most exacting methods of postoperative care.

SUMMARY AND CONCLUSIONS

Duodenal ulcer is primarily a medical problem. Approximately 80 per cent of the patients with this lesion respond to conservative measures.

Complications of duodenal ulcer demand surgical treatment. These are acute perforation, massive hemorrhage, cicatricial obstruction and intractability.

For the treatment of acute perforation, simple closure of the perforation is all that is indicated. This must be combined with proper after-care.

Massive hemorrhage from duodenal ulcer demands immediate hospitalization. Patients under 45 years of age will spontaneously cease to bleed with conservative treatment. At a time of election after complete recovery, subtotal gastrectomy is advised. Patients over 45 years of age are likely to bleed to death in spite of the best conservative care possible. Their condition should be carefully evaluated on admission and radical operation undertaken on many of them within seventy-two hours after the onset of bleeding. If delay beyond this period of time has occurred, then continuation of conservative treatment is indicated. The aged patient will rarely, if ever, withstand radical operation after a week or more of repeated bursts of bleeding and starvation.

Posterior gastroenterostomy, pyloroplasty and gastroduodenostomy are indicated only in the presence of scar tissue obstruction in aged patients.

Surgical cure of duodenal ulcer can be brought about only by subtotal gastric resection. This means the elimination of all the acid-activating cells in the antrum and a large proportion of the acid cells in the fundus. The operative mortality from this procedure has been reduced to a level compatible with the results obtained.

GASTRIC ULCER, BENIGN OR MALIGNANT

WALTMAN WALTERS, M.D., Sc.D.

ROCHESTER, MINN.

The morphologic characteristics and the evolution of most gastric ulcers are frequently unpredictable, and hence, in my opinion, most chronic gastric ulcers should be removed surgically without too much delay. After making such a bald statement, I should like to emphasize the fact that some small benign gastric ulcers and occasionally large ones may respond in an amazing fashion to a course of nonsurgical treatment. On the other hand, although many chronic gastric ulcers may seem to respond temporarily to a medical regimen, recurrence of the ulceration is frequent. This recurrence may be a new ulcer or a continuation of the original ulceration which did not heal but merely seemed to, and the recurrent lesion may be even larger and of more rapid growth than the original lesion. During this period, even while the patient has been on more or less of a medical regimen, fairly frequently there has been partial and sometimes almost complete physical disability. Were these the only disadvantages of delay in surgical treatment, there probably would not be much objection to a routine course of medical treatment before the decision whether or not surgical procedure should be carried out. The indecision relative to whether an ulcerating lesion of the stomach is benign or malignant places great responsibility on those who recommend methods of treatment other than removal of the lesion.

Although for years roentgenologists have emphasized that they cannot distinguish between benign and malignant gastric ulcer in a definite proportion of cases (about 10 per cent in the experience of the Mayo Clinic¹) and surgeons have called attention to the facts that a definite proportion of the patients operated on for cancer of the stomach had been reported by the roentgenologist to have gastric ulcer (also 10 per cent²) and that it is difficult and even impossible in many cases of ulcerating lesions of the stomach to distinguish grossly and by palpation between benign and carcinomatous ulcer, there are still some who believe that

From the Division of Surgery, the Mayo Clinic.

1. Gray, H. K.; Balfour, D. C., and Kirklin, B. R.: Cancer of the Stomach, *Am. J. Cancer* **22**:249-286 (Oct.) 1934.

2. Walters, W.; Gray, H. K., and Priestley, J. T.: Malignant Lesions of the Stomach: Importance of Early Treatment and End Results, *J. A. M. A.* **117**:1675-1681 (Nov. 15) 1941.

there is a triad of clinical findings and responses to nonsurgical treatment which is a criterion of benignancy. This triad consists of relief of symptoms, disappearance of the niche in the roentgenogram and disappearance of blood from the stools. If these three requirements are satisfied, it is assumed by some that the lesion has healed and hence was benign. The belief that this triad is indicative of healing or of benignancy has been shown to be erroneous by the frequently repeated reports of cases in which the triad was present but the lesions had not healed and were not benign.

In a symposium presented at the Ninety-Second Annual Session of the American Medical Association, June 6, 1941, Eusterman³ concluded as follows:

. . . It is apparent that gastric carcinoma not only may masquerade successfully as benign ulcer but may react to treatment in similar fashion as well.

In the discussion, Dr. Sara Jordan⁴ stated

. . . that neither the size of the ulcer nor the age of the patient nor the presence of normal acid or hyperchlorhydria should lessen our suspicion of carcinoma, for some of our largest lesions have been benign and some of the smallest malignant. and malignant lesions occur often enough in the young, and benign ulcers often enough in the middle aged and old, and acid is present often enough where the lesion is malignant, so that these three criteria of size of ulcer, age of patient and presence or absence of acid have no actual or practical value in the diagnosis of the individual patient.

Dr. Portis⁵ made the following statement:

. . . As I maintained years ago and still maintain, I would trust only the microscope in making this fine differential diagnosis. I still feel that gastric lesions, for the most part, are better handled by the surgeon. I am not discussing persons in their early twenties with a small, acute ulcer, but particularly that group of patients beyond 35 years of age who are good operative risks. I am convinced that the mortality and morbidity which would accrue in handling these early lesions surgically would be far less than a similar large series of cases handled medically.

I have chosen to quote extensively from this symposium because it gives the crystallized opinion of the internists who participated in that discussion, all of whom have passed through the stage in the latter part of the 1920's when practically all patients who had gastric ulcer were subjected routinely to medical treatment unless the lesion was large or

3. Eusterman, G. B.: Carcinomatous Gastric Ulcer: Misleading Results of Medical Therapy, *J. A. M. A.* **118**:1-5 (Jan. 3) 1942.

4. Jordan, S. M., in discussion on papers of Eusterman³ and Rafsky and Weingartner, *J. A. M. A.* **118**:10 (Jan. 3) 1942.

5. Portis, S. A., in discussion on papers of Eusterman³ and Rafsky and Weingartner, *J. A. M. A.* **118**:10 (Jan. 3) 1942.

the patient's pain such that it was difficult to control by nonsurgical methods. At that time I was particularly disappointed in this nonsurgical trend in the treatment of ulcerating gastric lesions because I was operating repeatedly on patients with carcinoma, many of whom had been treated for months for a suspected benign ulcer of the stomach or the duodenum because of similar histories and effective temporary responses to nonsurgical treatment before the recognition that the lesion was carcinomatous. Unfortunately, when some of these patients were operated on, it was found that the malignant lesion was no longer suitable for removal. Then there was another group of cases in my experience in which there was chronic gastric ulcer which was thought to be benign. However, when operation was performed, the lesion was found on microscopic examination to be carcinomatous ulcer or ulcerating carcinoma rather than benign ulcer. There was another group which seemed by virtue of age, smallness of lesion or response to medical therapy to have benign ulcer that seemed on roentgen examination to disappear. The patient, feeling well, was allowed to go home only to return months later either with benign ulcer larger than the original or with ulcerating carcinoma.

Recently (Dec. 22, 1941), I operated on 2 patients whose history and clinical picture, as well as the report of the roentgen examination of the stomach and the pathologic nature of the lesion after its surgical removal, seem to me to emphasize, when studied in parallel, some of the problems in making the preoperative diagnosis of ulcerating gastric lesion, and yet the indications for surgical treatment were apparent.

The first patient was a man aged 54 years. The crater of the gastric ulcer had increased from 1 to 2.5 or 3 cm. in diameter over a period of eleven months (fig. 1). This man had received a course of medical treatment in a hospital while he was registered at the clinic and had been sent home with the prescription of a diet for ambulant patients with ulcer. His history of stomach trouble dated over a period of only three and a half years. In addition to the gastric ulcer noted on both roentgen examinations, a duodenal ulcer was observed. Analysis of the gastric contents revealed a total acidity of 78 and free hydrochloric acid of 66 (Töpfer's method). Partial gastrectomy was performed on Dec. 22, 1941. The report of the pathologist indicated that 15 cm. of the stomach and 3 cm. of the duodenum had been resected. The stomach contained a simple ulcer (3 by 2.5 by 1 cm.) with marked eosinophilic infiltration, and there was an ulcer also in the duodenum.

In this case the increase in the size of the ulcer was surprising in view of the fact that the patient had been placed on a medical regimen for the treatment of the ulcer when he first was seen at the clinic on Aug. 6, 1940. At this time a roentgenogram of his stomach showed "hypertrophic gastric mucosa, two very small areas of ulceration in the lesser curvature at the angle of the stomach which may be associated with gastritis and also duodenal ulcer." He was given medical

treatment in the hospital between August 14 and August 25. On August 22 a roentgenogram of the stomach was negative; a duodenal ulcer was present. The patient was seen again on Jan. 15, 1941; at that time the gastric ulcer was barely demonstrable by roentgenogram. He was maintained on a regimen for ambulant patients with ulcer.

Except for the duodenum the roentgenogram of the second patient was similar to that of the first patient. A large perforating gastric ulcer was reported but



Fig. 1.—(a) Roentgenogram of the stomach taken Jan. 15, 1941, showing small gastric ulcer at the incisura; (b) roentgenogram of the stomach of the same patient, taken Dec. 18, 1941, showing large perforating gastric ulcer.

designated by the roentgenologist as probably malignant (fig. 2). This patient was 42 years of age and had had a history of stomach trouble for twenty years. Gastric acids varied from 40 to 18 and free hydrochloric acid from 10 to 0. Partial gastrectomy was performed on Dec. 22, 1941; at that time two thirds to three fourths of the stomach was removed. The pathologist reported that 15 cm. of the stomach was removed and contained an ulcerating and perforating grade 4

signet ring colloid adenocarcinoma (3 by 3 by 1 cm.) and that the carcinoma had extended through the gastric wall. No glandular involvement was observed. The striking feature in this case is that for a twenty year period the patient had a history of the type which I have referred to frequently as ulcer history; there had been no changes in that history in recent years, and still the lesion was found at operation to be grade 4 signet ring colloid carcinoma. One wonders what the lesion was that accounted for the patient's ulcer type of dyspepsia over such a long period and whether or not an ulcer preceded the formation of the ulcerating carcinoma.



Fig. 2.—Large perforating gastric lesion reported as gastric ulcer, probably malignant.

A critical analysis, however, of both these cases shows that a differential clinical diagnosis probably could have been made between the two lesions prior to operation, for the man who had carcinoma was reported to have a "gastric ulcer, probably malignant," by roentgen examination, and he had a low concentration of free hydrochloric acid on analysis of the gastric contents. Misleading, however, was his long history (twenty years) of ulcer dyspepsia. The patient who had the benign gastric ulcer had also a duodenal ulcer. However, the gastric ulcer increased in size under a regimen for ambulant patients with ulcer, and

the patient showed some symptoms of ulcer. In regard to the relation of gastric acids to benign and malignant gastric ulcer, Allen and Welch⁶ showed that free hydrochloric acid is present in about the same proportion of cases of benign gastric ulcer as of "ulcer-cancer." In a study of a series of cases of carcinoma of the stomach Gray, Priestley and I⁷ found that in approximately 50 per cent of the cases there was free hydrochloric acid, that in approximately 15 per cent the free hydrochloric acid values were more than 30 and that in 5 per cent they were more than 50.

Before leaving this discussion relative to the difficulty of distinguishing between some benign gastric ulcers and some carcinomatous ulcers, I should like to refer to a group of cases in which gastric ulceration, either benign or malignant, so interferes with the neuromuscular activity of the stomach that a marked degree of pylorospasm is set up and leads to the erroneous impression that the lesion is in the duodenum and is benign when in reality it is in the lesser curvature of the stomach and may be malignant. The presence of pylorospasm and barium sulfate in the lower part of the stomach may so mask the outline of the stomach that the presence of gastric ulceration may be overlooked entirely. I have reported from time to time several cases of this type.⁸ In many of them a so-called ulcer type of dyspepsia has been present, sometimes for as long as eight or twelve years. In cases in which pathologic examination of the ulcerating lesion proved it to be grade 4 (Broders' method) and highly malignant, the death of the patient within a year or two after resection seemed to be clinical confirmation of the highly malignant nature of the lesion.

To emphasize again that these cases are not rare but occur rather frequently, I should like to give a brief abstract of the record of 1 patient, a physician, whose case can be included in this group.

The patient, a man 55 years of age, registered at the clinic on Aug. 12, 1937. At that time a diagnosis of hemorrhagic duodenal ulcer with obstruction was made. The patient desired to try a course of medical treatment before resorting to surgical treatment and therefore went home. He returned on December 9, when the roentgen report was duodenal ulcer with obstruction and marked pyloric deformity. I operated on him on December 16, performing partial gastrectomy. There was a grade 4 ulcerated adenocarcinoma (3 cm. in diameter) situated on the lesser

6. Allen, A. W., and Welch, C. E.: Gastric Ulcer: The Significance of This Diagnosis and Its Relationship to Cancer, *Ann. Surg.* **114**:498-506 (Oct.) 1941.

7. Walters, W.; Gray, H. K., and Priestley, J. T.: Malignant Lesions of the Stomach: Results of Treatment in the Years 1907 to 1938, Inclusive, *Tr. West. S. A.* **50**:200-218, 1940; Malignant Lesions of the Stomach: Results of Treatment in the Years 1907 to 1938 Inclusive, *S. Clin. North America* **21**:1099-1115 (Aug.) 1941; footnote 2.

8. Walters, W.: Carcinoma of the Stomach, *Proc. Internat. Assemb. Inter-State Post-Grad. M. A. North America*, 1937, pp. 86-91; Surgical Lesions of the Stomach and Duodenum, *Texas State J. Med.* **34**:521-530 (Dec.) 1938.

curvature of the stomach immediately proximal to the pylorus. No glandular involvement was found. The patient returned to the clinic on March 27, 1939. Examination revealed recurrence of carcinoma with hepatic and supraclavicular metastatic growths. There was secondary anemia. Roentgen examination at this time showed the anastomosis to be free. The liver was larger than it had been formerly.

The trained gastroscopist has been helpful in describing the appearance of the lesion in the stomach. Even with the lesion observable, the possibility of misinterpretation by the gastroscopist of the pathologic nature of the ulcerating lesion must be emphasized definitely as a possible source of error. In spite of this, gastroscopy has been an important and necessary adjunct to recognizing the presence of intra-gastric lesions and observing their progress when they are treated by nonsurgical methods.

Several weeks ago I sent a patient into the hospital for three weeks' trial of medical treatment. Roentgen examination revealed a gastric ulcer high on the lesser curvature of the stomach and a duodenal ulcer. After the patient had been in the hospital for a week, the ulcer symptoms completely disappeared, and tests for blood in the stools gave negative results. At the end of the third week the roentgen examination was reported as showing disappearance of the lesion, but gastroscopic examination showed a small ulcerating lesion still present. In other words, had a gastroscopic examination not been made, the erroneous impression might have been reached that the ulcer had healed.

On the other hand, I operated recently on a patient who was suspected at home of having a malignant lesion of the stomach; yet roentgen examination on two occasions at the clinic failed to reveal the presence of a gastric lesion. Gastroscopic examination, on the other hand, was reported to reveal an ulcerating lesion high on the posterior wall of the stomach just off the lesser curvature. At operation both extragastric and intragastric exploration under visual control showed only hypertrophic gastritis with some spotty grayish exudate here and there between the hypertrophied gastric rugae.

These cases are exceptions; yet in both the patients were observed during the course of one month. They indicate that one cannot always rely implicitly on the roentgenogram in determining the changing character of a gastric ulcer and likewise that the gastroscopist's interpretation of his findings is subject to the same possibility of error that human beings apparently must always contend with.

The seeming disappearance of the crater in the roentgenogram or the decrease in size of the crater when the gastric lesion is malignant has been seen by Schindler⁹ to be due to the infiltration of the crater by the carcinomatous process originating in one edge of the ulcer, granulation tissue filling in the remainder. Eusterman³ stated that Rigler and Mallory made similar observations.

9. Schindler, R.: Early Diagnosis of Cancer of the Stomach: Gastroscopy and Gastric Biopsies, Gastrophotography, and X-Rays, *J. Nat. Cancer Inst.* 1:451-472 (Feb.) 1941.

CAUSES OF DELAY OF SURGICAL TREATMENT

I think I have shown the fallacy of the idea that all patients who have chronic gastric ulcerating lesions should be given a trial of medical treatment. The reasons for my viewpoint are the difficulty of distinguishing between chronic gastric ulcer and carcinomatous ulcer and the frequency with which gastric ulcers recur after nonsurgical treatment. Further, the argument that the risk of removal of a gastric ulcer carries a higher mortality rate than the risk of the lesions being malignant is not borne out by the fact. Certainly, during the past ten years, in which progress in American surgery has had no equal, the risk of operative procedures by well trained surgeons has decreased to a remarkable degree. I believe that the risk of removal of a gastric ulcer is not in excess of 5 per cent and that it is possible to operate on a large series of patients who have gastric ulcer with a mortality rate considerably less than that. In point of fact, partial gastrectomy was performed at the Mayo Clinic¹⁰ in 89 cases in 1939 with a mortality rate of 2.2 per cent and in 88 cases in 1940¹¹ with but 1 death. In addition, excision of the ulcer, with or without gastroenterostomy, was performed in 17 cases of gastric ulcer with no deaths. Operation was performed on 64 per cent of the patients suffering from gastric ulcer seen at the clinic in 1939 and on 61 per cent in 1940.¹²

From the standpoint of the possibility of recurrence of the ulceration, I have never observed benign gastric ulcer to recur or gastrojejunal ulcer to develop when half or more of the stomach, including the ulcer, had been removed.

Another argument sometimes used to avoid surgical removal of the lesion is that the ulcer is located so high on the lesser curvature that it might not be removable or could be removed only with great risk. In August 1940,¹³ I emphasized the point that gastric ulcers which appeared on roentgen examination to be located high on the lesser curvature were frequently not as inaccessible as they seemed to be, for at operation it was found that the perforation of the lesion into the capsule of the pancreas had so foreshortened the stomach above the lesion as to give an erroneous idea of the amount of stomach between

10. Priestley, J. T.; Gray, H. K., and Walters, W.: Report of Surgery of the Stomach and Duodenum, 1939, Proc. Staff Meet., Mayo Clin. **15**:707-717 (Nov. 6) 1940.

11. Gray, H. K.; Walters, W., and Priestley, J. T.: Report of Surgery of the Stomach and Duodenum for 1940, Proc. Staff Meet., Mayo Clin. **16**:721-727 (Nov. 12) 1941.

12. It may be interesting to compare the operability rate for gastric ulcer with that for duodenal ulcer. In 1939 at the clinic 18 per cent of the patients who had duodenal ulcer were operated on, and in 1940, 15 per cent.

13. Walters, W.: Cardial Gastric Ulcers: Results of Operation for Apparently Inaccessible Lesions, Arch. Surg. **41**:542-553 (Aug.) 1940.

the ulcer and the esophagus. In these cases there was actually more uninvolved stomach than the roentgenogram indicated. The early division of the gastrohepatic omentum at a high level assists in mobilizing the upper part of the stomach so that unusually high lesions can be removed without too great difficulty, especially when the original method of Billroth or the Hofmeister modification of the Polya operation is used, in which a greater portion of the lesser curvature (containing the ulcer) than of the body or the greater curvature is removed.

At that time Cleveland and I¹³ had studied a group of consecutive cases of cardial¹⁴ lesions in which operation had been performed during 1938 and 1939 at the clinic. Thirty-five of these patients with cardial benign gastric ulcers were operated on. Partial gastrectomy was done in 26 cases with 1 death, a mortality rate of 3.8 per cent. In 4 cases the ulcer was excised, and gastroenterostomy was performed. In 1 case excision of the ulcer alone was done, and in 4 cases gastroenterostomy was performed. In these 9 cases there were no deaths.

Personally, I believe that the ulcer can and should be removed in every case, even though it may be located so high on the lesser curvature of the stomach that it has to be removed by cautery puncture, or, if it is high on the posterior wall of the stomach, that transgastric excision is necessary.

Finsterer¹⁵ and Rieder¹⁶ have advocated the Kelling-Madlener type of subtotal gastrectomy which allows the ulcer to remain in situ when it is situated too high to be removed with safety. Lewisohn¹⁷ stated that he does not favor the Madlener procedure, for the postoperative results, when viewed in large numbers, are unsatisfactory. In my experience, in many of these cases the benign ulcer has healed after gastroenterostomy as reported by Eusterman and Balfour.¹⁸ The probable explanation of the healing of such an ulcer is the relative achlorhydria which occurs in such cases as the result of the gastroenterostomy from dilution and neutralization of gastric acids accomplished by reflux of biliary, pancreatic and duodenal secretion into the stomach through the gastroenteric stoma.

14. In this paper the adjective "cardial" is used in reference to the cardia, in contradistinction to "cardiac," which is generally used in reference to the heart.

15. Finsterer, H.: Das cardianahe Magengeschwür, *Wien. klin. Wchnschr.* **52**:394-400 (April 28) 1939.

16. Rieder, W.: Chirurgische Behandlung des kardanahen Ulcus ventriculi, *Arch. f. klin. Chir.* **196**:640-655, 1939; abstracted, *Internat. S. Digest.* **29**:21-22 (Jan.) 1940.

17. Lewisohn, R.: Problems in the Surgical Treatment of Chronic Duodenal Ulcers, *Ann. Surg.* **111**:355-361 (March) 1940.

18. Eusterman, G. B., and Balfour, D. C.: *The Stomach and Duodenum*, Philadelphia, W. B. Saunders Company, 1935, p. 259.

Personally, I have found the procedure of choice to be subtotal gastrectomy going well beyond the lesion and removing it. The advantages of this procedure are the removal of the lesion with its possibilities of hemorrhage, perforation or malignant degeneration, riddance of associated pylorospasm and decrease in the quantity and concentration of gastric acid secreted and stimulated, resulting in almost constant incidence of relative achlorhydria with almost total absence of gastrojejunal ulceration. The Polya type of end to side anastomosis posterior to the colon without enteroanastomosis is, in my opinion, preferable to anterior anastomosis. The Billroth I (Haberer) method of direct anastomosis as modified by Horsley and Haberer is used occasionally in selected cases.

The Billroth I type of anastomosis after partial gastrectomy is a satisfactory treatment of gastric ulcer and carcinoma in selected cases. It is particularly useful in instances in which the duodenum is mobile and the lesion is in the lower third or half of the stomach, for, under these circumstances, end to end anastomosis can be made without tension on the suture line. Clagett and I¹⁹ noted in a study of 272 consecutive operations for gastric ulcer performed at the clinic that this procedure was used 22 times in contrast to the posterior Polya operation, which was used 131 times. It should be emphasized that the results of the Billroth I procedure for gastric ulcer are satisfactory in a much higher percentage of cases than those of operations of a similar type for duodenal ulcer. This is probably due to the fact that the Billroth I operation produces a relatively high incidence of postoperative achlorhydria in cases of gastric ulcer and does not in cases of duodenal ulcer.

When the condition of the patient is such that removal of the lesion as a part of subtotal gastrectomy cannot be done without too great risk, then as safe a procedure as possible should be utilized which sufficiently reduces gastric acidity and reduces gastrospasm so that healing of ulceration may be anticipated. Surprisingly good results may be obtained by less radical methods, such as excision of the ulcer or cautery puncture with gastroenterostomy as advised by Balfour¹⁸ or occasionally by excision of the ulcer alone. Protection against further ulceration is accomplished by reduction of acidity by the gastroenterostomy. This was done 50 times with good results in the series of cases studied by Clagett and me. Eusterman and Balfour¹⁸ showed that 79 per cent of 100 patients on whom gastroenterostomy had been performed for gastric ulcer were well after five years. This procedure of low risk (3.9 per cent for 540 cases according to Eusterman and Balfour) is thus worthy of consideration when conditions make removal impossible. The

19. Walters, W., and Clagett, O. T.: The Surgical Treatment of Chronic Gastric Ulcer: Review of Two Hundred and Seventy-Two Cases, *Surg., Gynec. & Obst.* **71**:75-79 (July) 1940.

palliative resection of Madlener, in which also the ulcer is left behind, has not been utilized at the clinic.

Excision with knife or cautery may be done occasionally without gastroenterostomy, but it is not recommended because it does not offer an alteration of gastric physiologic conditions to prevent recurrence.²⁰ In an occasional case it has been utilized with good results. It does enable microscopic study of the lesion.

Similarly, segmental or sleeve resection may be done to remove the lesion, but disturbance of gastric peristalsis may follow in its wake, even to the extent of the development of an hourglass deformity due to contracture of the anastomosis. In addition, little change of gastric physiologic conditions is produced, and recurrent ulceration may occur. Segmental resection has been used with some success in selected cases, however, but not in recent years, and it is not to be recommended.

SUMMARY

The morphologic character and the evolution of gastric ulcer are frequently unquestionable. In 10 per cent of the cases, gastric ulcer is malignant. In many cases of chronic gastric ulcer, healing is temporary under nonsurgical methods of treatment, and recurrence of the ulceration is frequent.

In cases of ulcerating gastric lesions in which the patients are put on a medical regimen, gastroscopic examination should be used as an adjunct to roentgen examination to determine the effect of the nonsurgical regimen on the ulcer.

Clinical experience has shown that gastric carcinoma not only may masquerade successfully as benign ulcer but may react to nonsurgical treatment in similar fashion to benign ulcer as well. The clinical symptoms thought to be pathognomonic of benign gastric and duodenal ulcer have occurred in a third of the cases of carcinoma in which operation was performed at the Mayo Clinic, and in 80 per cent of this group there has been temporary effective response to a medical regimen.

Proper surgical treatment directed toward removal of gastric ulcer has been followed by excellent results. In my experience no recurrences have taken place when the surgical method of removing half of the stomach including the ulcer was employed, and in my experience this is the procedure of choice, although in an occasional case in which the ulcer is located high on the lesser curvature or the posterior wall, excision of the ulcer with gastroenterostomy has been followed by excellent results.

The operative risk in the removal of gastric ulcer should not exceed 5 per cent. In the hands of experienced surgeons the risk of partial gastrectomy with the removal of such lesions should not exceed 3 or 4 per cent.

20. Reduction of gastric acidity and relief of pylorospasm.

VITALLIUM CUP ARTHROPLASTY OF THE HIP

LENOX D. BAKER, M.D.

AND

CHESTER H. WATERS JR., M.D.

DURHAM, N. C.

When Venable, Stuck and Beach¹ introduced vitallium for use in orthopedic surgical procedures, this nonelectrolytic alloy was immediately employed in many forms. One of these was a cup to be used in arthroplasty of the hip joint.² In January 1939, Smith-Petersen³ reported the results of fifteen years of experimenting with mold arthroplasties and gave a preliminary report on the use of the vitallium cup as an interposing substance in arthroplasty of the hip. In his report he outlined the details of his approach to the hip joint and emphasized the importance of meticulous operation and the necessity for anatomic restoration of the hip joint. Since June 1939, twenty vitallium cup arthroplasties have been performed on 17 patients at Duke Hospital. Eighteen of these operations, with a follow-up period of from eight months to two years, are included in this preliminary report. One patient has not returned for follow-up examination, and another was operated on too late for his case to be included in this paper.

Before the results of the operations to be reported are analyzed, the conclusions reached by previous workers in this field of surgery should be reviewed. A variety of absorbable and nonabsorbable materials have been used as interposing substances for arthroplastic procedures. Plates of silver, magnesium, aluminum, gutta-percha and celluloid were first used; later animal membranes, such as pig bladder and the walls of ovarian cysts, were introduced as joint linings. Though muscle flaps and periosteal

From the Orthopaedic Division of the Department of Surgery, Duke University School of Medicine.

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1. Venable, C. S.; Stuck, W. G., and Beach, A.: The Effects on Bone of the Presence of Metals, Based upon Electrolysis: An Experimental Study, *Ann. Surg.* **105**:917, 1937.

2. Hopkins, H. H., and Zuck, F. N.: Arthroplasty of the Hip, with Use of Vitallium Cup, *M. Bull. Vet. Admin.* **15**:1, 1938.

3. Smith-Petersen, M. N.: Arthroplasty of the Hip, *J. Bone & Joint Surg.* **21**: 269, 1939.

flaps were inserted with only fair success, John B. Murphy⁴ developed the fascia flap method, which has served as a satisfactory basis for most of the modern arthroplastic procedures. Baer,⁵ Campbell,⁶ Putti,⁷ the MacAuslands⁸ and others outlined the various contraindications to arthroplasty and established standards by which to select cases and judge end results. In the selection of cases it was pointed out that the patient's general health must be good and his mental condition satisfactory for cooperation in a long and difficult convalescence. Putti stated, "We must therefore be prudent in proposing arthroplasty to a patient if we cannot thoroughly rely on his firmness of will to endure calmly the inevitable suffering and on his tenacious perseverance in the post-operative treatment." In addition to the patient's health, both physical and mental, his occupation and his ability to finance or to arrange for the financing of a long hospitalization must be considered.

Arthroplasty has been more successful in the presence of well preserved musculature, and better results have been reported from the treatment of bony ankylosis than from the treatment of fibrous ankylosis. It has been agreed that more effective results may be anticipated in the treatment of post-traumatic arthritis and of ankylosis following gonococcic infection. Arthroplasty for ankylosis following acute pyogenic infection has been found to be satisfactory provided that the disease process is completely quiescent and that eburnation or atrophy have not too greatly altered the bony structures adjacent to the joint. Albee⁹ pointed out the difficulties encountered in cases which show decrease in the abduction leverage because of shortening of the neck of the femur. Campbell,¹⁰ in outlining under fourteen headings the indications and contraindications for arthroplasty, counseled against using the procedure in cases of tuberculosis, emphasized the surgical maxim that all evidence

4. Murphy, J. B.: Arthroplasty, *Ann. Surg.* **57**:593, 1913.

5. Baer, W. S.: (a) Arthroplasty with the Aid of Animal Membrane, *Am. J. Orthop. Surg.* **16**:94, 1918; (b) Arthroplasty of the Hip, *J. Bone & Joint Surg.* **8**:769, 1926.

6. Campbell, W. C.: Arthroplasty of the Hip, *Surg., Gynec. & Obst.* **43**:9, 1926.

7. Putti, V.: Arthroplasty, *J. Orthop. Surg.* **3**:419, 1921.

8. MacAusland, W. R., and MacAusland, A. R.: *The Mobilization of Ankylosed Joints by Arthroplasty*, Philadelphia, Lea & Febiger, 1929.

9. Albee, F. H.: Original Features of Arthroplasty of the Hip and Knee, *J. A. M. A.* **101**:1694 (Nov. 25) 1933.

10. Campbell, W. C.: *Operative Orthopedics*, St. Louis, C. V. Mosby Company, 1939.

of acute infection must have subsided at least one year before operation and warned against the pitfalls to be expected in attempts at arthroplasty in joints affected by progressive arthritis.

Well aware of these definite contraindications and warnings, we attempted twenty arthroplasties on patients with the following types of arthritis: atrophic (4 cases: in 1 quiescent and in 3 active); Marie-Strümpell (8 cases: in 4 quiescent and in 4 active); pyogenic (4 cases); gonococcic (2 cases), and post-traumatic (2 cases). In classifying the results in these cases two methods have been used. The first of these is based on definite functional requirements and sets as the minimum for a good end result a painless stable hip with good weight-bearing alinement and at least 25 degrees of active flexion. The second classification is based on a comparison of the patient's condition before and after the operation. We feel that the comparative analysis of the individual case is the more important, since several of the cases in which we obtained our most satisfactory results have been placed under the poor results group according to the first method of classification. In analyzing the results of treating the badly crippled patient, it is important to consider whether the bedridden patient has been made ambulatory. If the patient was ambulatory before the operation, has his gait been improved, and has his pain been lessened? Can he sit more comfortably and with better cosmetic result? Does he walk with less support? Is he satisfied, and would he go through the same operation and long postoperative treatment for the same result? If these questions can be answered in the affirmative, the operation has been of value, even though the desired basic standard for a good result has not been met in every detail—"the result to the individual is the test."

REPORT OF CASES

CASE 1.—A young man 20 years of age had pyarthrosis, followed by fibrous ankylosis and 30 degrees' flexion deformity of nine years' duration. A Venable type cup was used for arthroplasty. His condition was satisfactory at discharge on the thirty-sixth postoperative day. He failed to report for follow-up treatment or examination until twenty-one months later. There was no motion, and he had 35 degrees' flexion and 10 degrees' adduction deformity. The result was poor.

CASE 2.—A 24 year old woman was bedridden with bilateral pyarthrosis of the hips of five years' duration. There were bony ankylosis on the right side and fibrous ankylosis on the left side without deformities. The muscle tone was poor, and there was bilateral genu recurvatum with instability. When last examined (the left hip twenty months, and the right hip fourteen months, after operation) both hips had active flexion of 25 degrees and were painless and stable. The result was good.

CASE 3.—An 18 year old woman had gonococcic arthritis of five years' duration. There were bony ankylosis and a 45 degree flexion-adduction deformity. A Venable cup arthroplasty was performed. Subcutaneous adductor tenotomy was performed at the time arthroplasty was done. The early postoperative course was uneventful. There were pain and elevation of temperature on the nineteenth postoperative day; subsequently, spontaneous drainage occurred. When cultured the drainage material yielded a growth of *Staphylococcus aureus*; inoculations into guinea pigs gave negative results. Continuous drainage was maintained. There was recurrence of the deformity. The cup was removed in March 1941, twenty-one months after arthroplasty; the articular surfaces were covered by smooth fibrous tissue. The result was poor.

CASE 4.—A man 22 years of age suffered from gonococcic arthritis of three years' duration. There were fibrous ankylosis, marked bony proliferation and a

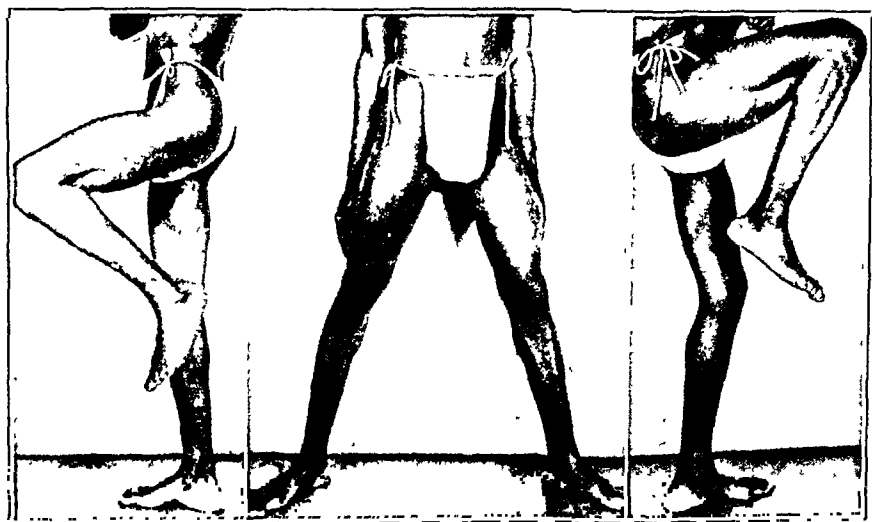


Fig. 1.—Photographs of the patient in case 4 twenty-one months after operation, showing the range of active flexion and the stability of weight bearing. The result was good.

45 degree flexion deformity. On examination twenty-one months after operation, the result was found to be good (fig. 1).

CASE 5.—A man 26 years of age had traumatic arthritis after fracture of the femur. The condition had endured for seven years. There was fibrous ankylosis in 10 degrees' adduction and the knee was ankylosed. A Venable cup arthroplasty was performed. Twenty-four months after operation there was no motion, and there was a 35 degree flexion and 25 degree adduction deformity. The result was poor.

CASE 6.—A man 37 years of age had a slipped epiphysis with traumatic arthritis of twenty-five years' duration. The head of the femur was large and flat; the acetabulum was shallow, and there was no deformity. There was a history of alcoholism; delirium tremens occurred on the third postoperative day. The opera-

tive wound disrupted, and there occurred self contamination with subsequent infection. Drainage was maintained for ten weeks. Twelve months after operation there were 20 degrees of motion and a stable hip. The result was poor (fig. 2).

CASE 7.—A man 23 years of age had active Marie-Strümpell arthritis of twelve years' duration with involvement of the hips and the knees of four years' duration. There was bony ankylosis on the right side in 10 degrees' flexion and 20 degrees' adduction; there was fibrous ankylosis on the left side in 20 degrees' flexion and 30 degrees' abduction. The spine was ankylosed. The general musculature was poor. Arthroplasty was performed. A Venable cup was used in the right hip and a Smith-Petersen cup in the left. When the patient was last examined (the right hip twenty-two months, and the left seventeen months, after operation), there was no motion or deformity. The result was poor.

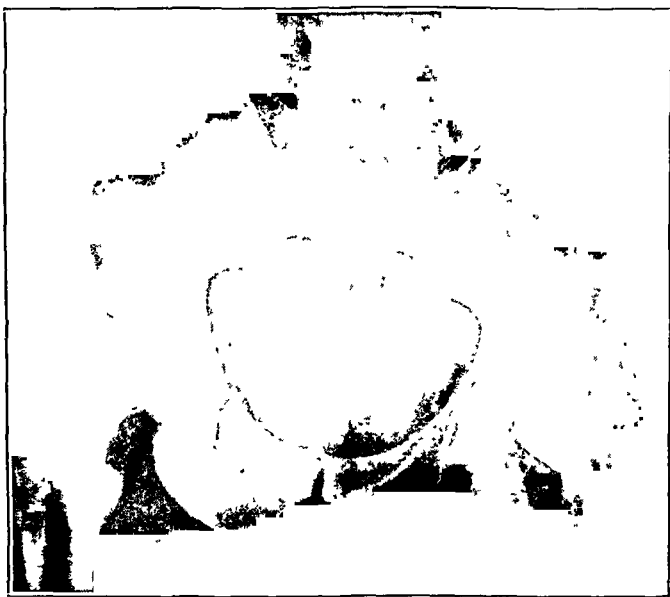


Fig. 2.—Roentgenogram of the patient in case 6 one year after arthroplasty, showing bony proliferation about the cup. The patient had a postoperative infection, and drainage was maintained for ten weeks. There was marked fibrosis in the soft parts, which resulted in 20 degrees flexion deformity. At the time of writing the hip is painless and has 20 degrees of motion; there is a gluteal gait. The result was classed as poor, but the patient is showing gradual improvement.

CASE 8.—A man 25 years of age had active Marie-Strümpell arthritis of seven years' duration. There was fibrous ankylosis in 45 degrees' flexion. The entire spine was ankylosed and the motion in the opposite hip was limited. There were pain and limitation of motion in the hip not subjected to operation. Seventeen months after operation there was 30 degrees of active flexion; the hip was stable, and there was no deformity. The result was good.

CASE 9.—A man 28 years of age had inactive Marie-Strümpell arthritis of six years' duration. There was fibrous ankylosis in 45 degree flexion and 15 degree

abduction. The spine was solidly ankylosed. Subcutaneous adductor tenotomy was performed at the time arthroplasty was done. Cellulitis at the site of tenotomy appeared seven weeks after operation without complication. Seven months after operation there were 25 degrees of active flexion and slight pain. The result was fair.

CASE 10.—A man 29 years of age was bedridden with inactive Marie-Strümpell arthritis of three years' duration. There was bony ankylosis in both hips; in the right hip there was 25 degrees' flexion and 10 degrees' adduction. The spine was solidly ankylosed. In the left femur there was old fracture with 3 inches (7.6 cm.) shortening; in the knee there was 10 degrees' motion. The musculature was poor. Thirteen months after operation the patient wished operation on the opposite hip; there was 40 degrees' flexion, and the hip was stable and painless. The result was good.



Fig. 3.—Roentgenogram of the patient in case 11 taken fourteen months after operation, showing ankylosis of the sacroiliac joints and the lumbar spine. At the time of writing restoration of the hip joint is satisfactory; the patient has 90 degrees of active flexion, walks with a stable hip and has no pain.

CASE 11.—The patient was a man 30 years of age with active Marie-Strümpell arthritis of fifteen years' duration. There had been involvement of the hip for five years; there was fibrous ankylosis in 40 degrees' flexion and 20 degrees' abduction. The entire spine was ankylosed. Fourteen months after operation there was 90 degrees' flexion, and the hip was painless and stable. The result was good (fig. 3).

CASE 12.—A man 34 years of age had inactive Marie-Strümpell arthritis of twelve years' duration. Fascial arthroplasty had been done on the right side. There was fibrous ankylosis on the left side. A Venable cup arthroplasty was done on the left side. A rubber drain was used for forty-eight hours. Postoperative infection occurred on the third day. The cup was removed six months after opera-

tion; the articular surfaces were covered by smooth fibrous tissue. In the right hip (the one on which fascial arthroplasty had been done) thirty-two months after operation there were 45 degrees' passive flexion and 15 degrees passive abduction with crepitus and pain. In the left hip twenty-two months after operation there were 35 degrees' passive flexion and 10 degrees' passive abduction with pain; the hip still continued to drain. Roentgenograms showed good joint space. The result was poor.

CASE 13.—A woman 31 years of age had inactive atrophic arthritis of fifteen years' duration. Fascial arthroplasty was done on the right side in 1932. There was fibrous ankylosis on the left side with 30 degrees' flexion deformity. The

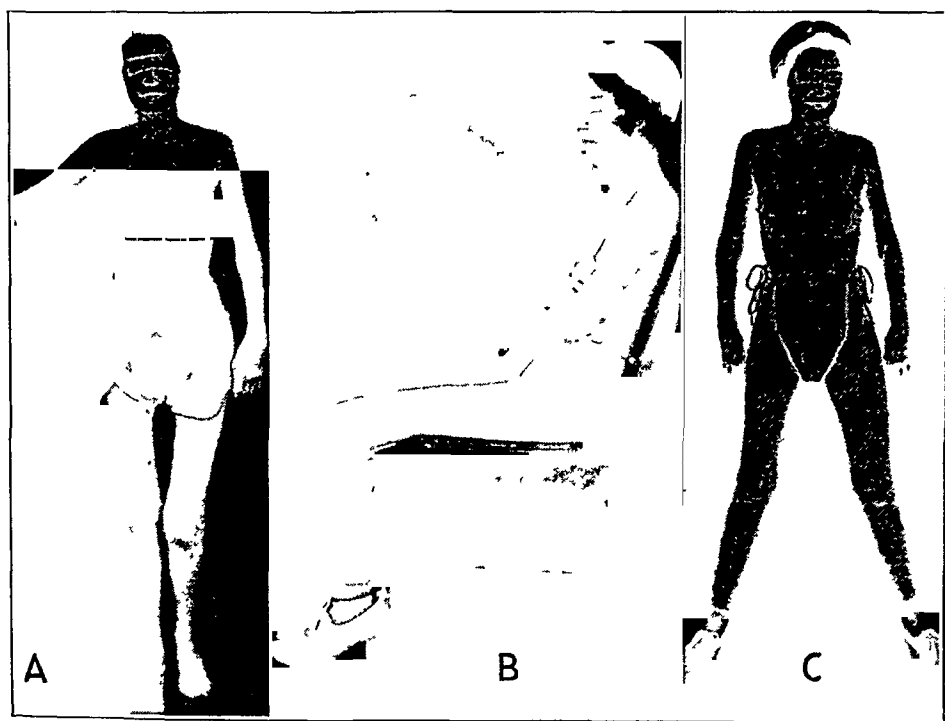


Fig. 4.—*A*, photograph of the patient in case 13 seven years after fascial arthroplasty of the right hip, showing flexion and adduction deformity of the left hip. *B* and *C*, photographs taken eighteen months after vitallium cup arthroplasty of the left hip. At the time of writing the patient walks without support with some bilateral gluteal gait. Note the arthritic changes in the hands.

spine was ankylosed. All peripheral points were involved. When examination was made eighteen months after operation on the right side, the result was good (fig. 4).

CASE 14.—A woman 39 years of age was confined to a wheel chair with active atrophic arthritis of fifteen years' duration. The hips had been involved for five years. In the right hip there were fibrous ankylosis, mild flexion and adduction deformity and poor musculature. Subcutaneous adductor tenotomy was per-

formed at the time arthroplasty was done. Fourteen months after operation there was 35 degrees' active flexion, and the hip was painless and stable. The result was good.

CASE 15.—A 40 year old woman had been bedridden for one year. She had active atrophic arthritis of six years' duration and bilateral fibrous ankylosis of the hips without deformity. The spine was ankylosed, and the knees were painful. Convalescence after the first arthroplasty (done on the left side) was complicated by generalized exacerbation of the arthritic process without involvement of the hip on which operation had been performed. When last examined (the left hip eighteen months, and the right hip eleven months, after operation) the patient's arthritis was active; there was generalized joint pain, and the hips were least symptomatic but painful. The result was fair (fig. 5).



Fig. 5.—Photographs of the patient in case 15, who was bedridden with active atrophic arthritis one year before the first operation, showing the good range of motion eleven and eighteen months, respectively, after bilateral cup arthroplasties. There has been improvement in the general condition; the result was classified as poor because of pain, although the pain in the hips is not as marked as in the other joints.

COMMENT

In considering postoperative complications we have noted, as did Gill,¹¹ that any persistent postoperative limp, disability or deformity appears to be due largely to adduction and flexion of the thigh associated with insufficient mobility. Fibrosis about the site of operation resulting in contractures in the soft tissues has caused us a great deal of concern, and it has been most difficult, even with traction, to prevent flexion-

11. Gill, B, in discussion on Baer.^{7b}

adduction deformities. After our most recent operation we used a plaster spica on the opposite extremity in an effort to control the pelvis and maintain adequate abduction and extension in the hip on which operation was performed. Adjustable posterior plaster sleeping shells in which the adduction can be controlled have been a part of the routine treatment.

In 1 patient in whom infection was present, calcification in the soft parts resulted in marked bony proliferation (fig. 2). Because of too short a femoral neck or possibly as a result of postoperative absorption of the neck, 2 patients had a bony bridge form across the new joint line. The cup was removed in 2 cases because of infection; in both instances the head of the femur and the acetabulum presented smooth glistening surfaces.

SUMMARY AND CONCLUSIONS

Our series of cases is too small to warrant any definite conclusions. Our impressions are these:

Too much emphasis cannot be placed on the necessity for meticulous operation and the importance of anatomic restoration of the hip joint.

There must be an adequate period of hospitalization and intelligent cooperation in the after-treatment.

Because of weakness of the gluteus medius muscle, inability to maintain abduction during weight bearing is a frequent postoperative complication.

Fibrosis is likely to occur in the soft parts, with resultant deformity and loss of motion.

It is difficult to predict an end result on the basis of the causation of ankylosis. Of the eighteen operations, eleven were on joints affected by atrophic arthritis or Marie-Strümpell disease. In this group the results of five were good, of three fair, and of three poor (the results of one were poor because of infection). On the pyogenic, the traumatic and the gonococcic joints, there were seven operations. The results of three were good and of four poor (the results of two were poor because of infection).

There has been no indication of any tissue reaction to the cup, and, in those hips for which arthroplasty is indicated, vitallium is a satisfactory interposing substance.

The operation is of particular value for bedridden and badly crippled patients.

Dr. R. Beverly Raney assisted in the clinical work on which this paper is based.

ABSTRACT OF DISCUSSION

DR. MARIUS N. SMITH-PETERSEN, Boston: The principle of this procedure is to insert an impermeable mold in which nature can do its repair work. It was originally intended that this mold be removed; this would leave two benign congruous surfaces, mechanically able to perform the functions of a normal joint. If physiologic repair is expected, physiologic conditions must be created. Fascia

lata arthroplasty did not succeed in bringing this about; a mechanically imperfect joint was created which might function satisfactorily for a time, but it seldom survived for long.

The mold arthroplasty is an attempt to imitate nature's original normal joint. A movable joint is created; in that joint the head of the femur moves inside the mold, and the mold moves inside the acetabulum. This must be kept in mind at the time of operation. The operation does not simply consist of slipping a mold over a partially molded head; the head must be smoothly finished, and the cup must fit the head, so that there will be an excursion of motion between the head and the mold. When the surgeon thinks that he has finished the operation, time and again he will find that his operative time will be lengthened because on testing the motion of the joint he finds that the motion is not as it ought to be: The cup may get caught in the acetabulum; there may be a little projection in the acetabulum that should be removed. There may be no motion between the head and the mold because of imperfect molding of the head. If the surgeon meets such conditions, he must not feel that he has been operating for a long time already and so must hurry; he must not say, "I guess I will let well enough alone."

If he makes his approach correctly, following structural planes with a minimum amount of bleeding, the patient should not be in shock by the time the hip joint is exposed. This is the time when the operator must be careful and slow in creating really congruous and mechanically perfect joint surfaces. Attention must be paid to the acetabulum as well as to the head; if the acetabulum is imperfect, the joint cannot be expected to function well. I am sure that in my earlier cases I did not pay enough attention to the acetabulum; I did not remove enough bone to make the cup freely movable in the acetabulum.

This operation is extensive and difficult. Every surgeon who contemplates doing it should practice on cadavers and see other surgeons who have had experience with it before he undertakes it.

The postoperative treatment is prolonged; much patience is required of both the surgeon and the patient. The surgeon should be sure to inform the patient beforehand that this procedure does not mean that he merely has to submit to an operation and then be handed a new joint on a silver platter. It demands cooperation between the surgeon and the patient if good results are to be obtained.

Dr. Baker stated that a stable hip with 25 degrees of motion is a good result. There must be more than 25 degrees of motion, even though the hip is stable; 25 degrees of motion means interference and impingement and, consequently, pain.

DR. G. MOSSER TAYLOR, Los Angeles: I wish to discuss another use for the vitallium cup. Mention has been made of the use of the vitallium cup in reconstruction operations for hip joints. I have 2 cases to present in which Whitman reconstruction of the hip joint was done with the use of the vitallium cup. In the past the biggest objection to reconstruction operations has been the pain. As far as stability of the hip is concerned this operation is satisfactory, but the persistent postoperative pain has left much to be desired. For this reason, the vitallium cup was tried.

In the first case, four procedures were done. First, a Whitman cast was used. After three months internal fixation was done. A year later a Bracket operation was attempted, but it failed. About the only thing left to do then was to fuse or to remove the head of the femur and insert a vitallium cup. The cup fitted over what was left of the neck of the femur without further reconstruction. The result has been at least fair. The hip is stable, furnishes efficient weight bearing and gives the patient little discomfort. There are flexion of 90 degrees and flexion

contracture of 20 degrees; there is abduction of 10 degrees. There is no adduction, but there is rotation of 10 degrees, with, however, a shortening of $1\frac{1}{2}$ inches (3.8 cm.). Power in this case is not good. The patient is unable to balance herself on this leg. However, she does all her housework, and is well satisfied with the results.

In the second case reconstruction was done seven months after failure of internal fixation. Because there is less fibrosis, owing to the fact that there were fewer procedures, the results have been better. There are flexion of 110 degrees and normal extension, but there is no flexion contracture. There are both abduction and adduction as well as rotation. There is a shortening of only 1 inch (2.5 cm.). The patient is able to balance herself on this leg. Her limp is definite, but she has little discomfort—only stiffness and aching after rest. She walks five or six blocks at a time, does her own housework and enjoys fairly good freedom.

DR. HUGH SMITH, Memphis, Tenn.: My series of fifteen monarticular vitallium cup arthroplasties performed on 15 patients is far too small a series from which to draw conclusions. In general I am disappointed with the end results. These have not compared favorably with one hundred and fifty-seven fascial arthroplasties, the majority of which were carried out on solidly ankylosed hips secondary to pyogenic infection or trauma. In this group only 25 per cent failures were expected; consequently, I still lean toward fascial arthroplasty for patients of this type.

On the contrary, cups seem to offer definite improvement in the treatment of malum coxae senile, hypertrophic arthritis, old slipped upper femoral epiphysis and aseptic necrosis of the head of the femur after trauma. While I have not performed any bilateral cup arthroplasties for atrophic arthritis, my experience with thirty-seven bilateral fascial arthroplasties leads me to believe that no method will effect a high percentage of satisfactory results.

The most disappointing feature of cup arthroplasty is the tendency toward excessive periarticular fibrosis. Patients treated by arthroplasty who two months after operation were making satisfactory progress in increase of motion have regressed to an unsatisfactory range at four to six months. Three cups have been removed and the hips manipulated at three, nine and sixteen months, respectively. This procedure has been followed by a material improvement in function. In the future I expect to remove all cups, on the assumption that a permanent metallic joint surface cannot be physiologic, regardless of how well it may be tolerated.

My attitude at present is neither one of indiscriminate condemnation nor one of unqualified enthusiasm. Rather I wish to maintain a state of openminded, liberal indecision until my experience and that of others is more extensive.

DR. CARL E. BADGLEY, Ann Arbor, Mich.: I am surprised that Dr. Baker should select primarily cases of arthritis for the use of the vitallium cup. I think, as Dr. Smith-Petersen has said, that the arthritic joint is the worst type of joint on which to employ arthroplasty, regardless of whether the old method or the method of the vitallium mold is used. I am surprised also at the report of Dr. Smith that a traumatic lesion of the hip is better treated by fascial arthroplasty than by the vitallium cup. I have had a series of about 60 to 75 cases in which vitallium cup arthroplasty was done. This treatment of aseptic necrosis of the hip after traumatic dislocation or after fracture of the neck of the femur has given not 25 per cent flexion, which the authors accept as a successful result, but an almost unrecognizable fault in the hip with an excellent range of motion and an excellent gait (except that all have a gluteal gait; this, however, is obviated by the trick movement that all the patients soon learn, that of kicking off with the achilles tendon). Similarly, congenital dislocations of the hip, the old ones with displacement, have done remarkably well with treatment by vitallium cup.

arthroplasty. In several cases of fracture dislocation of the acetabulum an excellent range of motion has been obtained, with a gait that would defy almost any one to diagnose as hip difficulty.

The attitude of patients after arthroplasty with the vitallium mold, their comfort the day after operation and their ability to move the hip are so entirely different from those of patients after fascial arthroplasty that there is no comparison. I had 2 cases of spondylitis rhizomelica in which I had successful results in treating the right hips by fascial arthroplasty and equally successful results in treating the left hips by vitallium arthroplasty. The end result with fascial arthroplasty was achieved in one year in both of these cases. The end result with vitallium cup arthroplasty (comfort, motion to 90 degrees and good abduction) was obtained in less than four months. These patients were out walking in three months' time, with considerable relief and considerable motion. The time is greatly lessened by the use of vitallium arthroplasty.

In treating an infectious or a proliferative process, as in cases of atrophic arthritis, there will be trouble whether vitallium cup arthroplasty or fascial arthroplasty is used because there is a regeneration of the capsule. It is of the greatest importance that the cup be long enough to extend to the margin of the vastus muscles so that there will be no exposure of the neck and so that capsular adhesion to the neck cannot occur. In cases of arthritis in which another operation was required after vitallium cup arthroplasty because of increased stiffening of the hip, I have always found that the capsule was glued to the neck. That was the failure of the Venable cup, which, with its flanges, allowed a space through which the capsule could become glued, through these openings to the neck.

The use of the vitallium cup is one of the most efficient steps in arthroplasty of the hip that I have seen.

DR. LENOX D. BAKER, Durham, N. C.: Dr. Smith-Petersen has reemphasized the importance of the patient's cooperation. He has pointed out also the importance of meticulous operation, especially in shaping the head of the femur and the acetabulum. Dr. Waters and I feel that the most careful work should be done on the soft parts as fibrosis has been the main difficulty in our unsatisfactory cases.

We believe, too, that it is necessary to have a freely movable surface on both sides of the cup; this is shown by the fact that we now use the Smith-Petersen cup. However, it has been of interest to us that in both instances in which Venable cups have been removed the articular surfaces were smooth on the head of the femur as well as in the acetabulum.

Dr. Taylor presented another use for the vitallium cup, but according to our classification, the results in his 2 cases would be classed as poor because the patients gave positive reactions to the Trendelenburg test.

Dr. Badgley questioned our selection of cases of arthritis. We said in the paper that we were fully aware of the contraindications and the importance of the proper selection of cases. We had eighteen cases; 10 of these were cases of arthritis. In 6 of these the results were good; in 4 they were poor (in 1 they were poor because of infection). There were 7 cases of pyogenic, gonococcic or traumatic joints. In 3 the results were good; in 4 they were poor (in 2, because of infection). We feel that the vitallium cup procedure has a marked advantage over the fascial arthroplasties in that it offers some hope to the badly crippled patient with arthritis.

LEG-SHORTENING OPERATION FOR EQUALIZING LEG LENGTH

M. BECKETT HOWORTH, M.D.

NEW YORK

Unequal leg length has always been an important and common orthopedic problem. It may be due to any of a variety of causes and in a large proportion of cases can be prevented. Joint dislocation, shortening or overgrowth of one bone or of the whole extremity may be responsible. Congenital dislocation of the hip is the most common cause of unequal leg length in infancy, but congenital shortening or absence of one or more bones may occur. Congenital dislocation can usually be corrected by early reduction. Suppurative arthritis of the hip, especially if drainage is delayed, often results in partial or complete absorption of the femoral head and neck, or partial or complete dislocation of the hip, with resultant shortening. Such shortening can usually be prevented by early adequate drainage of the original focus and of the joint and chemical treatment of the infection. Arthritis or osteomyelitis may sufficiently damage the epiphysial disk to disturb growth, especially if drainage is delayed. A fracture with angulation or overriding may cause shortening of a leg, although the modern treatment of fractures promises to eliminate this cause. War injuries with immediate or surgical removal of masses of bone may result in serious shortening. Congenital coxa vara, coxa plana, and slipping of the upper femoral epiphysis may result in some shortening, although early recognition and prevention have greatly reduced the incidence of shortening due to slipping of the femoral epiphysis. Hemiatrophy and hemihypertrophy account for occasional cases of leg inequality; included in the group due to hemihypertrophy are cases of arteriovenous aneurysm, hemangioma and neurofibromatosis. Surgical treatment of aneurysm and operation or radiotherapy for hemangioma may limit the shortening. Tumors requiring bone resection may result in shortening unless bone grafting can be used. Infantile paralysis is still the most common source of shortening of the leg in this country, and no preventive method has been found, although growth of the longer leg can be limited. Prevention of the disease itself or of the

From the New York Orthopedic Dispensary and Hospital.

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accompanying paralysis offers greater promise for the future. Thus shortening is far more common than elongation of the leg and can in many cases be prevented.

EFFECTS OF LEG INEQUALITY

Inequality of leg length of less than an inch (less than 2.5 cm.) causes little or no assymetry of the body or limp and rarely any discomfort. It may be an advantage to patients with certain types of scoliosis, a stiff extended knee, a stiff abducted hip, weak hip abductor muscles, a long leg brace or talipes equinus. A difference of 1 or 2 inches (2.5 or 5 cm.) usually causes a noticeable limp and assymetry of the body, but this difference can be easily corrected by tilting the pelvis or elevating the heel and possibly the sole of the shoe. An inequality of 2 inches (5 cm.) or more prevents the patient from standing with the legs together unless the hip and the knee are flexed on the long side and consequently interferes with the patient's walking, running, dancing and sports. Compensation is possible with a cork-soled shoe or patten and in cases of marked shortening, with a double shoe or extension brace; however, these devices are clumsy, expensive and unsightly. Scoliosis, a deformed and ankylosed hip or knee, or weak leg or trunk muscles may further complicate marked leg inequality, while the faulty mechanics of the short leg may cause pain in an unstable lumbosacral joint, hip or knee. Accordingly, it is desirable to prevent leg inequality so far as it is practical and to correct the inequality when the amount of shortening and the degree of disturbance warrant correction. Associated deformities should usually be corrected before the shortening operation is undertaken; for example, subtrochanteric osteotomy for hip adduction deformity should be performed before leg shortening is attempted.

METHODS OF CORRECTION

There are several methods of minimizing or correcting leg inequalities. The simplest procedure is the stimulation of the growth of the epiphysis of the shorter leg by drilling or the insertion of irritants or the retardation of the growth of the longer leg by roentgen irradiation. Unfortunately, none of these methods has been uniformly or sufficiently successful, and none can be accurately controlled, but the possibilities of such treatment have not been exhausted. The growth of the longer leg may be slowed by obliterating an epiphysial disk by the operation of Phemister or one of its modifications, or growth may be essentially stopped by obliterating all of the epiphyses. This operation is relatively simple and safe and is certainly the method of choice for the growing child, even if only partial correction is obtained. The difficulty of

judging the proper time for the operation and the number of epiphyses to treat has been partly eliminated by use of the formulas obtained from a number of studies of leg growth in children and relation of these formulas to the height of other members of the family. Probably no exact method, infallibly applicable in each case, will be discovered for determining the eventual length of the leg. Should epiphysial exeresis



Fig. 1.—N. H., a girl 14 years of age, had a tuberculous hip. The leg was $4\frac{3}{4}$ inches (12 cm.) short. Two inches (5 cm.) was resected with 1 inch (2.5 cm.) step cut osteotomy and intramedullary peg fixation. Slight separation of fragments occurred with 15 degrees recurvatum and 15 degrees varus deformity. *A*, immediately after operation; *B*, five months after operation.

fail to equalize the leg length, the short leg may be lengthened directly by osteotomy followed by traction in a special apparatus such as the one first described by Putti and modified by Abbott. Leg lengthening has the advantage of restoring the affected bone or leg to normal length

and the patient to normal height without risking damage to the "good" leg. It is less suitable if the long leg is the abnormal one, if the patient is tall or if the short leg is considerably affected by paralysis, atrophy or deformity. The operation is technically difficult and beset with complications, and the convalescent period is long. It is not my province to discuss it further here.

Finally, unequal leg length may be partly or completely corrected by shortening the longer leg. Legs have been accidentally shortened by fracture with overriding since the beginning of vertebrate life. It has long been known that considerable shortening may occur with only temporary reduction in muscle or joint function. Deliberate controlled shortening by osteotomy with overriding or bone resection is natural and logical.

HISTORY OF LEG-SHORTENING OPERATIONS

In 1847, Rizzoli reported a femoral osteotomy with overriding of the fragments for correcting leg inequality; and Mayer, in 1850, and Sayre, in 1863, each reported a similar case. No other mention of the operation has been found until 1907, when Glaessner¹ reported 2 and Deutschländer² 3 cases in which the operation of Heine was used. Deutschländer fixed the fragments with an aluminum plate and two screws. In 1916, Taylor³ mentioned experiments on cadavers with plates, mortises and intramedullary and transfixion pegs. In 1917, Shands⁴ reported a case in which resection was done and wire suture was used. In 1918, Calvé⁵ described three methods of fixing the femoral fragments: (1) by mortise and tenon, (2) by impacting the tenon into the medullary cavity of the upper fragment and (3) by a double mortise and tenon. He reported 2 cases in which he had used the third operation. In 1918, Fassett⁶ described the use of a Lane plate in 3 cases, and a tongue and groove osteotomy in 1. In 1923, Royle⁷ reported 4 resections with which intramedullary pegs were used

1. Glaessner, P.: Die Kontinuitätsresektion der langen Röhrenknochen zur Ausgleichung von Verkürzungen, *Ztschr. f. orthop. Chir.* **30**:39, 1908.

2. Deutschländer, C.: Die Heinische Operation der Kontinuitätsverkürzung zwecks Ausgleichung von Längendifferenzen der unteren Gliedmassen, *Ztschr. f. orthop. Chir.* **19**:47, 1908.

3. Taylor, R. T.: Shortening Long Legs and Lengthening Short Legs: A New Surgical Procedure, *Am. J. Orthop. Surg.* **14**:598, 1916.

4. Shands, A. R.: Shortening the Long Leg, *Internat. J. Surg.* **30**:273, 1917.

5. Calvé, J., and Galland, M.: A New Procedure for Compensatory Shortening of the Unaffected Femur in Cases of Considerable Assymetry of the Lower Limbs (Fractures of the Femur, Coxalgia, etc.), *Am. J. Orthop. Surg.* **16**:211, 1918.

6. Fassett, F. L.: An Inquiry into the Practicability of Equalizing Unequal Legs by Operation, *Am. J. Orthop. Surg.* **16**:277, 1918.

7. Royle, N. D.: The Treatment of Inequality of Length in the Lower Limbs, *M. J. Australia* **1**:716, 1923.

and 1 with which a Lane plate was employed. In 1926, Ritter⁸ mentioned resection with the use of intramedullary pegs.

The first shortening of the tibia and the fibula was described by Brooke⁹ in 1927 with a report of 2 cases. He used a tibial inlay graft after resection, and he described a step cut osteotomy of the femur, in which beef bone screws were used for fixation. In 1931, Groves¹⁰ described 2 cases in which the intramedullary tenon method of Calvé was used, and in 1933, Moore¹¹ added 13 cases in which a similar operation

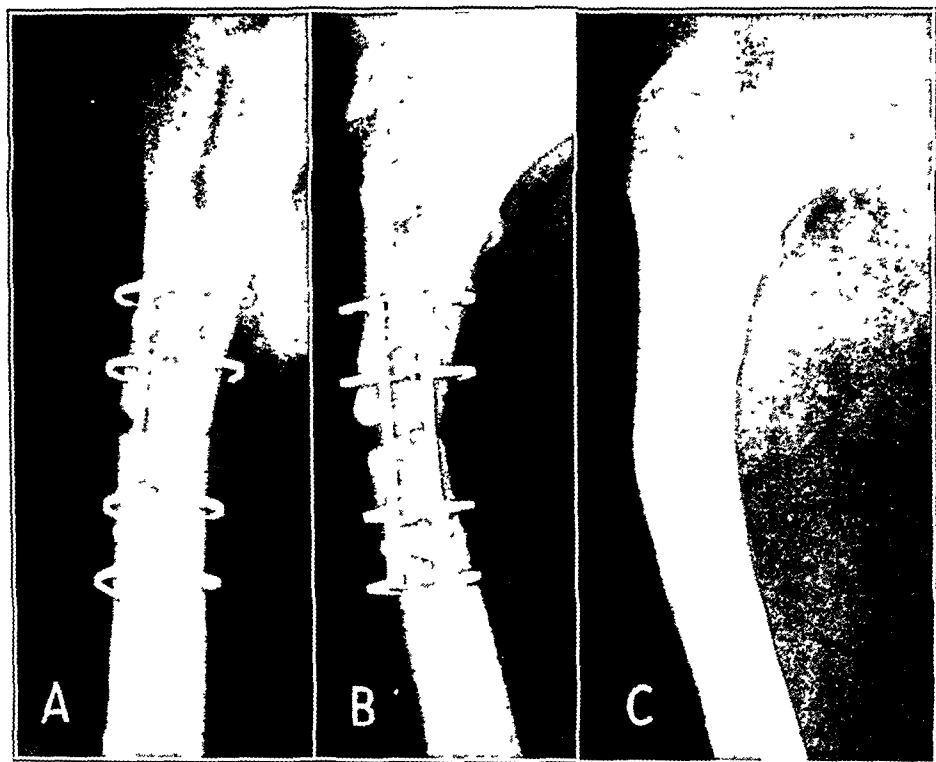


Fig. 2.—H. C., a young man 17 years of age, had a tuberculous hip. The leg was 5 inches (12.7 cm.) short. Two and a half inches (6.4 cm.) was resected, and intramedullary peg and Smith clamp fixation was done. There was 15 degrees varus deformity. Three months after operation the clamp was removed. *A*, immediately after operation; *B*, three months after operation; *C*, three years and ten months after operation.

8. Ritter, R. O.: Technique of Equalizing Leg Length, *Surg., Gynec. & Obst.* **43**:93, 1926.

9. Brooke, J. A.: Shortening of Bones of the Leg to Correct Inequality of Length, *Surg., Gynec. & Obst.* **44**:703, 1927.

10. Groves, E. W. H.: An Address on Stature and Poise: The Problem of Unequal Legs, *Brit. M. J.* **2**:1, 1931.

11. Moore, J. R.: Tibial Lengthening and Femoral Shortening, *Pennsylvania M. J.* **36**:751, 1933.

was performed. In 1933, Camera¹² reported the first large series, 32 cases in which the condition was treated by resection and the use of a diamond-shaped intramedullary peg. In 1935, White¹³ reported 45 cases of osteotomy with overriding. In the first cases he fixed the fragments with wire bands; later he fixed them with two transfixion pins protruding through the wound. In 1936, Brooke¹⁴ reported 4 cases (2 of the tibia and fibula) in which Lane plates were used, making a total in the literature of 10 cases in which plates were used. In 1940, Harmon and Krigsten¹⁵ reported the use of an intramedullary peg with onlay grafts. Thus the leg has been shortened by osteotomy with overriding, resection or step cutting, and the fragments have been fixed by various types of intramedullary or transverse pegs, onlay or inlay grafts, mortise and tenon, or tenon with intramedullary impaction, wire sutures or metal plates.

OPERATION AT THE NEW YORK ORTHOPAEDIC DISPENSARY AND HOSPITAL

The leg-shortening operation was first used at the New York Orthopaedic Dispensary and Hospital in 1928 by Dr. H. L. Von Lackum, who shortened the femur of a 20 year old woman with infantile paralysis 3 inches (7.6 cm.) by a step cut osteotomy with the insertion of an intramedullary bone peg. In the following twelve years (to December 1940), 16 more osteotomies were done for shortening the femurs of 15 patients.¹⁶ In the first case, although the legs were equalized, subsequent reduction and fusion of the subluxated hip on the opposite side were done, which required a 1 inch (2.5 cm.) shortening of that leg. The patients ranged in age from 13 to 23 years, the average age being 18 years. Two of the patients were boys, and fourteen were girls. The cause of the shortening was tuberculosis of the hip in 6 cases, tuberculosis of the knee in 1, infantile paralysis in 5, suppurative arthritis of the hip in 2, congenital dislocation of the hip in 1 and Ollier's disease

12. Camera, U.: 32 casi di accorciamento dell'arto inferiore sano a scopo ortopedico: indicazioni, tecnica, risultati, *Chir. d. org. di movimento* **17**:569, 1933; Le raccourcissement opératoire du membre inférieur sain dans la grande boiterie due à l'inégalité de longueur des deux membres, *Bull. et mém. Soc. d. chirurgiens de Paris* **24**:247, 1932.

13. White, J. W.: Femoral Shortening for Equalization of Leg Length, *J. Bone & Joint Surg.* **17**:597, 1935.

14. Brooke, R.: Bone Shortening for Inequality of Length in the Lower Limbs, *Proc. Roy. Soc. Med.* **30**:441, 1937.

15. Harmon, P. H., and Krigsten, W. M.: The Surgical Treatment of Unequal Leg Length, *Surg., Gynec. & Obst.* **71**:482, 1940.

16. Dr. B. P. Farrell worked on the early cases and encouraged the preparation of this study.

in 1. These patients desired the leg shortening because of the limp, the necessity of wearing a raised shoe and the associated assymetric and undesirable appearance of the foot and leg. Pain was of little consequence. Partial disability for walking, running, work and play was a factor in most of the cases. The long leg was usually completely sound except for minor involvement in the patients with infantile paralysis.

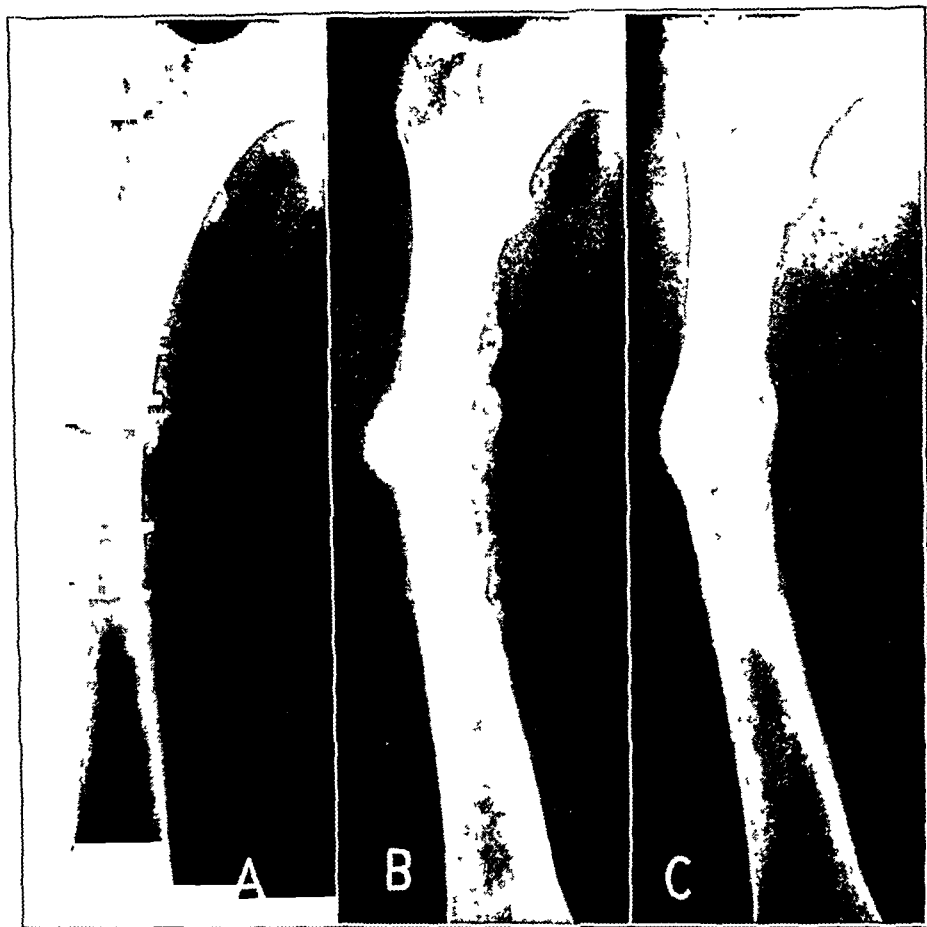


Fig. 3.—S. P., a young woman 18 years of age, had a tuberculous hip. The leg was 4 inches (102 cm.) short. Two and three-eighths inches (6 cm) was resected, and intramedullary peg and Smith clamp fixation was done. The callus was fractured when the cast was removed three and a half months after operation. The clamp was removed. There was 15 degrees varus and recurvatum deformity. A, three and a half months after operation; B, four and a half months after operation; C, eight and a half months after operation.

TECHNIC OF OPERATION

The first 3 operations were osteotomies with resection and end to end (2 cases) or step cut (1 case) apposition; 2 were in the midshaft with an intramedullary peg, and 1 was supracondylar. In the first case 10 degrees valgus and 10 degrees

recurvatum of the fragments occurred in the plaster spica, with partial separation and $\frac{1}{4}$ inch (0.6 cm.) overriding of the fragments, but union was not delayed. The supracondylar osteotomy resulted in 20 degrees varus and 15 degrees recurvatum of the fragments with $\frac{1}{4}$ inch (0.6 cm.) overriding due to posterior displacement of the lower fragment, but prompt union occurred. The third osteotomy was followed by 15 degrees recurvatum, with $\frac{1}{4}$ inch (0.6 cm.) separation of the fragments, and 10 degrees varus, while the osteotomy line persisted for nearly six months. Due to the difficulty in controlling the alinement and the contact of the fragments in the first 3 operations, a Smith clamp, as well as an intramedullary peg, was used for the next 3 femurs (1934). Slight separation of the fragments occurred in 1 case, and 15 degrees angulation in the other two, while solid union required five to eight months. In view of these difficulties, the use of the 5 inch (12.7 cm.) six screw Lane plate was begun in November 1934. The old style plate was used in the first case, with tapered screws through only one cortex; a gap of $\frac{3}{8}$ inch (0.96 cm.) and valgus of 10 degrees were present between the fragments, but solid union resulted. The newer type vanadium steel plate was used in each of the following 10 cases, with a step cut Z osteotomy near the midshaft. The femur was shortened $1\frac{3}{4}$ to $3\frac{1}{2}$ inches (4.5 to 8.9 cm.), (average, $2\frac{1}{2}$ inches [6.4 cm.]). The prongs of the step cut were $\frac{1}{2}$ to $2\frac{1}{2}$ inches (1.3 to 6.4 cm.) long, (average, 1.6 inches [4 cm.]). One plate broke on removal of the spica at four months and was removed, but solid union was present one month later. A second plate, applied with 5 degrees angulation and $\frac{1}{4}$ inch (0.6 cm.) separation of fragments, broke at five months, allowing closure of the gap followed by prompt union; this plate was removed at seven months, but union was not mature until one year after the shortening. The remaining plates were well applied, and solid union occurred in from three to six months, with unsupported weight bearing at five months. Onlay grafts from the resected bone were used in addition to the plate in 1 case; a large mass of callus resulted, but union was no more rapid than in the other cases.

The technic of the leg-shortening operation is as follows: The midfemur is exposed by an anterolateral incision through the vastus lateralis and vastus intermedius muscles. Osteotomy is done with drill holes and osteotome or with a circular or reciprocating saw. It is important when a motor saw is used to avoid burning the bone or leaving it glassy smooth. The step cut may be made before or after the femur is divided and the fragments fitted accurately together. The plate is shaped to fit the fragments closely without force. The fragments and the plate are held apposed with Lambotte, Heitz-Boyer or Jackson clamps while holes are drilled perpendicularly through the plate holes and both cortices of the femur. The drill is of the exact diameter of the shaft of the screw (exclusive of threads). Self-tapping untapered screws are used, threaded from end to end. They are driven carefully, to avoid stripping the bone threads as the tapping is done, and yet snugly. The screw should be just long enough to penetrate the opposite cortex when the screw is set. It is preferable to have two (or more) of the screws traverse both tongues of the step cut, and the screws should pass at least $\frac{1}{4}$ inch (0.6 cm.) from the cut ends. The fragments should be firmly held on completion of the plating. These principles of plating have been adopted from the fracture service of Darrach and Murray at the Presbyterian Hospital in New York. It is planned in the future to use the stainless steel plates recommended by them. Their modified Lane technic has not been used because the leg short-

enings are done on nontraumatized tissues, but care and gentleness are considered most important.

A double spica from the midthorax to the toes of the affected side was used in most cases, but a single spica may be used for a thin person, particularly if the hip is fused. The spica is removed for roentgen treatment at the end of three months and is usually left off; the patient is allowed a week or two in bed for the return of muscle power and joint motion; then walking without weight bearing is begun with a walker or crutches. Massage, heat and underwater and other exercises are used for several weeks after the plaster is removed.

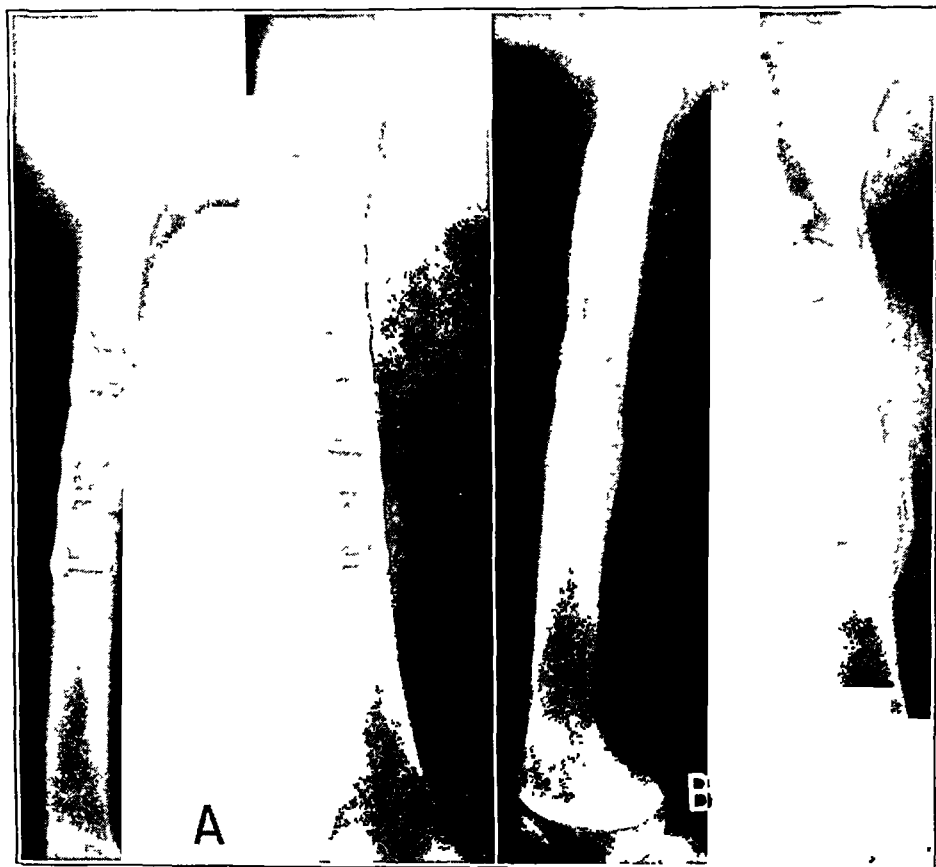


Fig. 4.—E. V., a girl 13 years of age, had tuberculosis of the left knee, which had previously been resected. The leg was $7\frac{1}{2}$ inches (19 cm.) short. The left tibia was lengthened $2\frac{5}{8}$ inches (6.7 cm.). One inch (2.5 cm.) resection of the right femur was done, and there was an overlapping of $2\frac{1}{2}$ inches (6.4 cm.). Excellent alinement of the plate and the fragments was obtained, and solid union occurred in three months. *A*, three months after operation; *B*, six months after operation.

RESULTS

These 16 patients (with 17 femoral shortenings) have been followed for one to eleven years (average, four and a half years). There were no infections of wounds, no deaths and no nonunions. The 1 case in which a poorly applied plate held the fragments apart until the plate broke

may be considered an instance of delayed union. Two of the early unplated femurs had an overriding of $\frac{1}{4}$ inch (0.6 cm.). Angulation of 5 to 15 degrees occurred in 7 cases, but plates were used in only 2 of these. Hip and knee motion and muscle power returned to normal within six months after operation in every case. The residual leg inequality varied from nothing to 2 inches (5 cm.), averaging $\frac{1}{2}$ inch (1.3 cm.). In 1 case, in which there was a total shortening of $7\frac{1}{2}$ inches (19 cm.), the opposite tibia and fibula were lengthened $2\frac{1}{2}$ inches (6.4 cm.), while the femur was shortened 3 inches (7.6 cm.). The limp was greatly reduced or eliminated in all cases but 1; the patient in this case was a girl with extensive poliomyelitis who felt that she had not benefited by the operation. Built-up shoes were discarded in all but 2 cases, and in these the lift was reduced. The appearance of all patients was improved, and none complained of shortened stature. Capacity for walking and more strenuous activities was usually improved; several of the patients were able to participate in all sports. Thus 11 cases of successful leg shortening with step cut osteotomy and Lane plate are added to the 10 cases of simple osteotomy or resection with the use of some type of plate reported in the literature. The same technic, possibly with transverse instead of step cut osteotomy, should be equally applicable to the tibia. However, in most cases all or most of the shortening occurs in the femur, and since it is desirable to have the knees opposite each other for appearance as well as mechanical efficiency, it is preferable to shorten the bone which is relatively longer.

INDICATIONS

The leg-shortening operation usually shortens the height of the patient less than the length of the bone removed. If the patient stands with the legs straight without a lift, the shortening of the body is only half the shortening of the leg, as the pelvic tilt is corrected and the opposite leg remains the same. If the patient must stand on the short leg with the knee and hip of the long leg flexed, the body height is not less after the shortening, as the longer leg is then merely straightened. If the subject wears a raised shoe and changes to a regular shoe after the operation, the height is reduced by the amount of the lift. A short person can partially make up for the shortening by wearing higher heels. Removal of several inches from the leg may cause a noticeable shortening of the legs in relation to the trunk. Since most people sit most of their waking hours and leg shortening does not affect the sitting height, there is little disadvantage to most persons in losing 1 to 3 inches (2.5 to 7.6 cm.) of standing height. The physical advantage of lowering the center of gravity (noted by White), especially when the leg is weak, the improvement in walking and other physical activities, as well as the removal of a built-up shoe, more than offset the loss of height. The

operation is not a simple one and must be done with precision and minimal risk of infection or nonunion, but it is a far simpler and safer procedure than leg lengthening. The step cut osteotomy with bone plating offers an accurate method of shortening the femur and maintaining good alinement. Solid bony union occurs in a reasonable time,

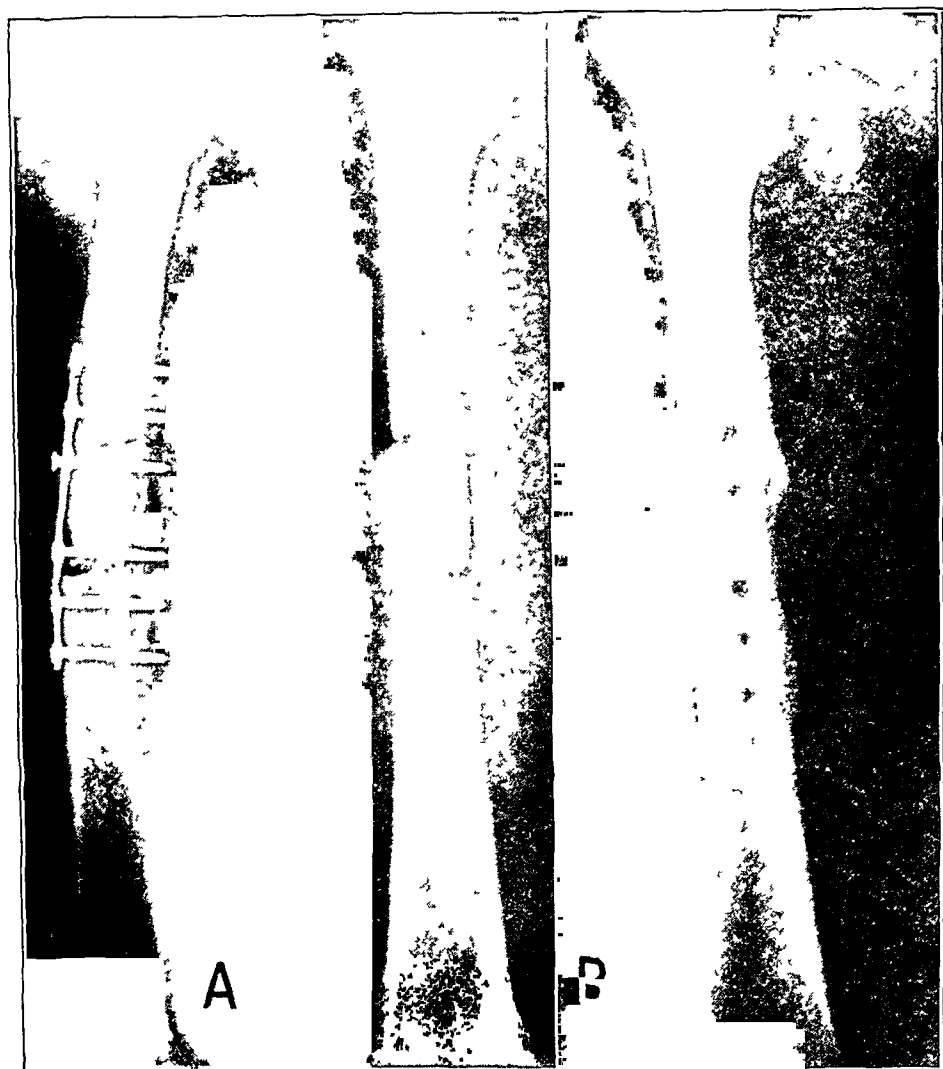


Fig. 5.—M. B., a girl 15 years of age, had a congenitally dislocated hip. The leg was $2\frac{1}{2}$ inches (6.4 cm.) short. One inch (2.5 cm.) resection was done with an overlapping of $1\frac{1}{2}$ inches (3.8 cm.); thus $2\frac{1}{2}$ inches (6.4 cm.) shortening was obtained. A vanadium steel plate was used, but the apposition of the fragments and the plate was imperfect. Fracture of the plate and the callus occurred on removal of the cast three months after operation. The plate broke four months after operation and was removed at five months. Prompt union of the fragments followed. *A*, three months after operation; *B*, five months after operation.

and there is a minimum of interference with muscle and joint action. The operation is rarely applicable to children under 12 years of age, because

of the difficulty in predicting the exact difference in adult leg length and total height, and the greater simplicity of epiphysial exeresis. This technic should be suitable for certain types of war injuries to the bones of the leg. Before the operation is undertaken, all the important factors such

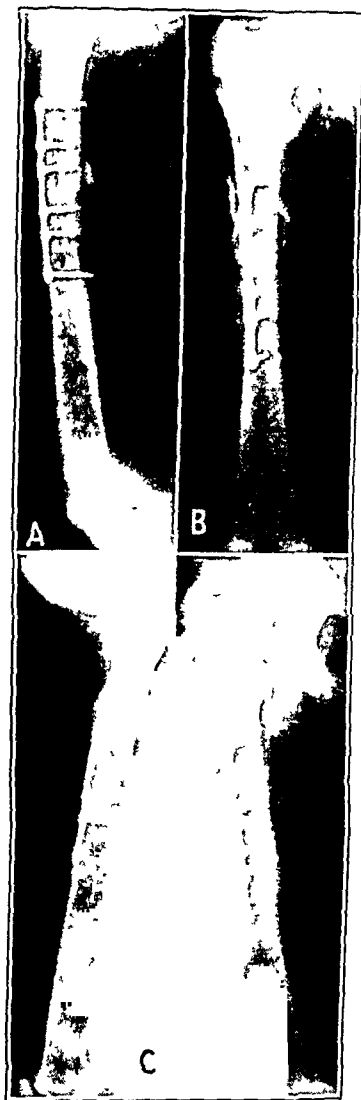


Fig. 6.—R. C., a girl 15 years of age, had infantile paralysis. The leg was $3\frac{1}{4}$ inches (8.3 cm.) short. There was an overlapping of 3 inches (7.6 cm.). A vanadium steel plate and several small onlay grafts were used. Probably the fastest and most solid union in the entire series occurred in this case. *A* and *B*, immediately after operation; *C*, five months after operation.

as age, sex, occupation total body height, leg length discrepancy, associated deformity, weakness, ankylosis and physical performance should be evaluated.

SUMMARY AND CONCLUSIONS

The causes, prevention and effects of leg inequality are discussed, and the methods of correction are briefly described and evaluated. The history of the leg-shortening operation is given, including the different methods of shortening the bone and of fixing the fragments.

Seventeen leg-shortening operations are reported, including 11 step cut osteotomies with Lane plate fixation. The technic of the operation and the postoperative care are described.

The results of the 17 operations are good. Infection or nonunion has not occurred. The effect of the shortening is discussed.

The step cut osteotomy with Lane plate fixation is recommended as an effective and precise method of shortening the leg and securing prompt and strong union of the fragments.

ABSTRACT OF DISCUSSION

DR. JOSEPH A. FREIBERG, Cincinnati: I think it is generally understood that the indications for leg shortening—leg equalization—are definite but that the number of cases is relatively small. This is evident from the fact that in a clinic such as Dr. Howorth's there were only 17 cases during a period of twelve years.

There are many pros and cons as to the choice of method. It has always appealed to me and to a number of men that one of the better methods of leg shortening entails the simplest operative procedure and leaves in no foreign material. I refer to Dr. J. Warren White's method of stripping the periosteum, overlapping the bones after osteotomy and holding them with simple wire pins which extend through the wound and are later to be removed. This has the advantage that the bones are never held apart and there is always bony contact. In the beginning, until the overlapping bone fragments are partly absorbed and alined in the healing callus, the result will appear rather crude on roentgen examination. Nevertheless, I do not believe any prettier end results can be seen than those shown by Dr. Howorth.

In Cincinnati the Phemister procedure is used to a great extent because the majority of children treated are still growing and by the time they reach the end of their growth period, when this procedure cannot be done, the difference in leg length in any number of cases is small.

TRANSPLEURAL ESOPHAGOGASTROSTOMY

REPORT OF A SUCCESSFUL CASE

A. F. JONAS JR., M.D.

OMAHA

A malignant tumor at or near the junction of the esophagus and the stomach when operable is best treated by transpleural resection and esophagogastrostomy. Such an operation permits wide extirpation of the growth and the regional lymphatics and allows the patient later to swallow and pass food into the stomach in a normal manner. Since Voelcker¹ in 1908 successfully performed esophagogastrostomy after abdominal resection of a carcinoma of the cardiac end of the stomach, the operation has been successfully performed in 21 additional cases. A good summary of the literature on the subject was published in 1938 by Adams and Phemister.² In 1941 Garlock³ gave an account of his clinical experience with the problem. The procedure hereinafter reported follows closely the method described in 1940 by Carter, Stevenson and Abbott.⁴

In the past the operation has more often resulted in failure, with death from shock or infection, than in success. Accordingly, it may be of importance to consider a few technical details. The patient, often greatly debilitated, must be brought into the best possible preoperative condition. In cases of complete obstruction jejunostomy for feeding is indicated. Preliminary pneumothorax allows the wide exposure necessary and provides sufficient room for work within the pleural cavity. The operation must be sufficiently radical to extirpate the regional lymph nodes at the cardioesophageal junction. However, too much of the esophagus cannot be mobilized, or its segmental blood supply will be destroyed and mediastinitis eventuate. The anastomosis must be so made that cicatricial stenosis will not result. The stomach, the upper

From the Department of Surgery, Johns Hopkins University School of Medicine and Johns Hopkins Hospital.

1. Voelcker: Ueber Extirpation der Cardia wegen Carcinoms, Verhandl. d. deutsch. Gesellsch. f. Chir. **37**:126, 1908.

2. Adams, W. E., and Phemister, D. B.: Carcinoma of the Lower Thoracic Esophagus, J. Thoracic Surg. **7**:621, 1938.

3. Garlock, J. H.: The Problem of Carcinoma of the Cardiac End of the Stomach, Surg., Gynec. & Obst. **73**:244, 1941.

4. Carter, B. N.; Stevenson, J., and Abbott, O. A.: Transpleural Esophago-Gastrostomy for Carcinoma of the Esophagus and for Carcinoma of the Cardiac Portion of the Stomach, Surgery **8**:587, 1940.

end of which is left in the thorax, should be anchored securely to a rib so that the suture line will be subjected to no tension. After the thoracic operation, abdominal gastrostomy for feeding should be done if preliminary jejunostomy has not previously been carried out. However, preliminary gastrostomy should never be done, for it seriously limits the mobility of the stomach so that this organ cannot be drawn up into the chest. Food and drink should not be allowed by mouth for at least a week, and during the first postoperative days swallowed saliva should be aspirated from the esophagus by means of a small indwelling tube, for Dragstedt⁵ has shown that in dogs with experimental esophageal obstruction the saliva overflows from the full esophagus into the bronchial tree and gives rise to pneumonia. The generous administration of blood, plasma or intravenous fluid to combat shock is of course necessary. Chemotherapy should be employed; at present the drug of choice is sulfathiazole (2-{paraaminobenzenesulfonamido}-thiazole).

REPORT OF CASE

D. P., a 43 year white farmer, was admitted April 14, 1941, complaining of difficulty in swallowing of eight months' duration. On taking solid foods he experienced pain beneath the xiphoid process and promptly regurgitated. He was able to swallow liquids, particularly warm ones, with little discomfort but during his illness had lost about 30 pounds (13.6 Kg.). Roentgenograms had been made, and the patient had been told that he had cardiospasm.

Physical examination showed evidence of marked loss of weight but scarcely any dehydration. A small supraclavicular node was palpated on the left side. The temperature, the pulse rate and the respiratory rate were normal. Examination of the urine yielded negative results. The Wassermann test was negative. The blood pressure was 114 systolic and 84 diastolic. The hemoglobin content was 98 per cent. The white blood cell count was 8,800. A roentgenogram made after a barium sulfate meal showed a filling defect involving the lower 2 inches (5 cm.) of the esophagus and a large portion of the cardiac end of the stomach. Esophagoscopy examination demonstrated the same obstruction at the lower end of the esophagus, but no biopsy could be made.

Under local anesthesia the supraclavicular node was removed for biopsy, and was reported normal. On April 17, the abdomen was explored with the patient under anesthesia induced with avertin with amylene hydrate, nitrous oxide and ether. Through an upper midline incision a hard round tumor the size of an English walnut was felt at the junction of esophagus and stomach. No regional lymph nodes were palpable, and the liver was free from metastases, but the tumor lay so high that no part of the esophagus was available for intra-abdominal anastomosis. Accordingly, the wound was closed without further intervention.

On April 24, 1,000 cc. of air was introduced into the left pleural cavity; on April 26, another 1,000 cc. Subsequent roentgenograms showed almost complete pneumothorax on the left but no mediastinal shift. On April 28, with the patient under anesthesia induced with avertin with amylene hydrate and ether, operation was carried out; intratracheal positive pressure was used. A left thoracotomy through

5. Dragstedt, C. A., and Mullinix, R. B.: Experimental Esophageal Obstruction, *Arch. Surg.* 24:152 (Jan.) 1932.

the seventh intercostal space was extended from the midscapular to the midaxillary line, and the left lung was observed to be about 60 per cent collapsed. After the inferior pulmonary ligament was divided and the phrenic nerve was crushed, the diaphragmatic fibers were split from the esophagus to the lateral chest wall. This afforded a good view of the tumor. A few small nodes were palpable in the nearby fat. The stomach was next drawn through the rent in the diaphragm, and the left gastric and left gastroepiploic vessels were ligated. After the field had been carefully packed off with moist gauze pads, the stomach was divided

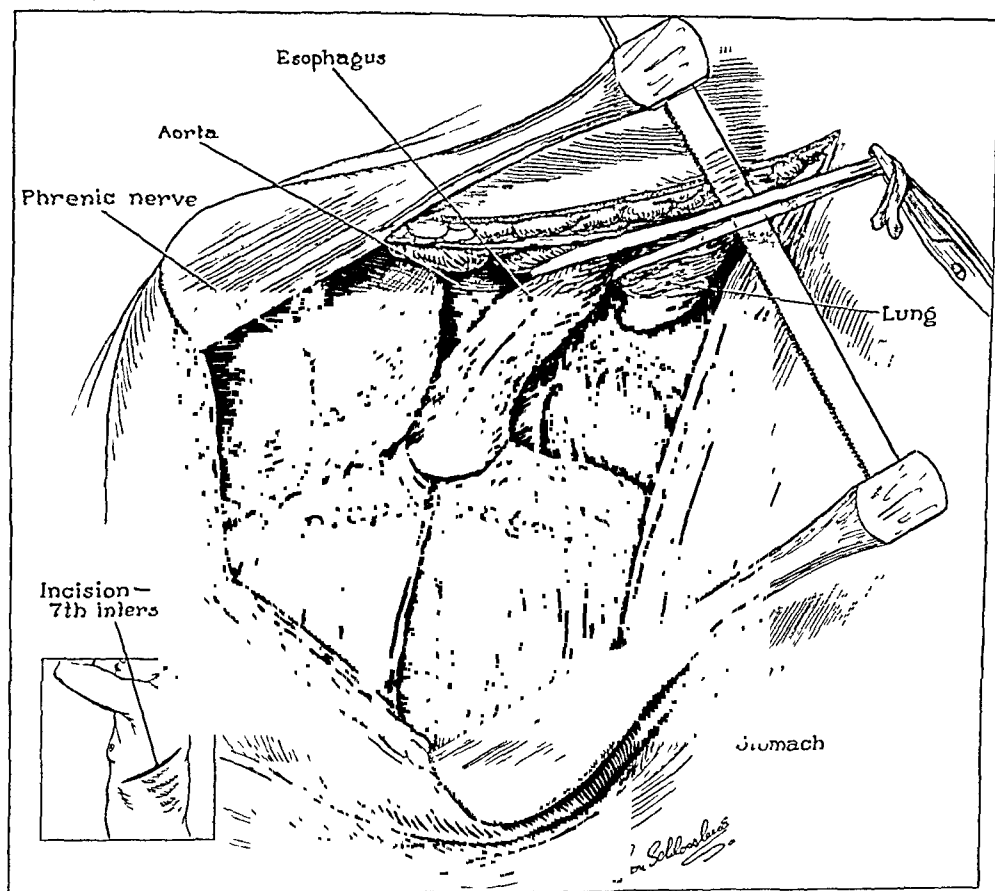


Fig. 1.—Through a posterolateral approach in the seventh interspace, the esophagus is grasped and the diaphragm split.

transversely between two Payr clamps placed an inch (2.5 cm.) below the lesion. The stomach was then closed with a continuous transfixion suture of chromic catgut reinforced by a number of inversion silk sutures. The lower part of the esophagus was similarly divided and ligated with plain catgut, and the tumor was removed. Two transverse incisions were made on the anterior wall of the stomach; the upper was an inch (2.5 cm.) below the line of closure, and the lower was an inch farther down. Through the upper one, the tied end of the esophagus was thrust, and through the lower, its ligature was brought out in order to keep the esophageal opening well within the stomach during the suturing, which was carried out with

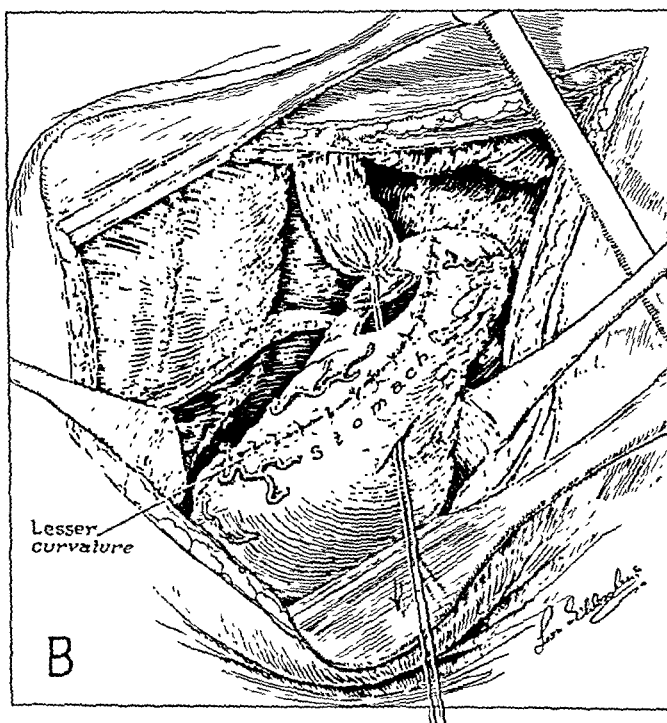
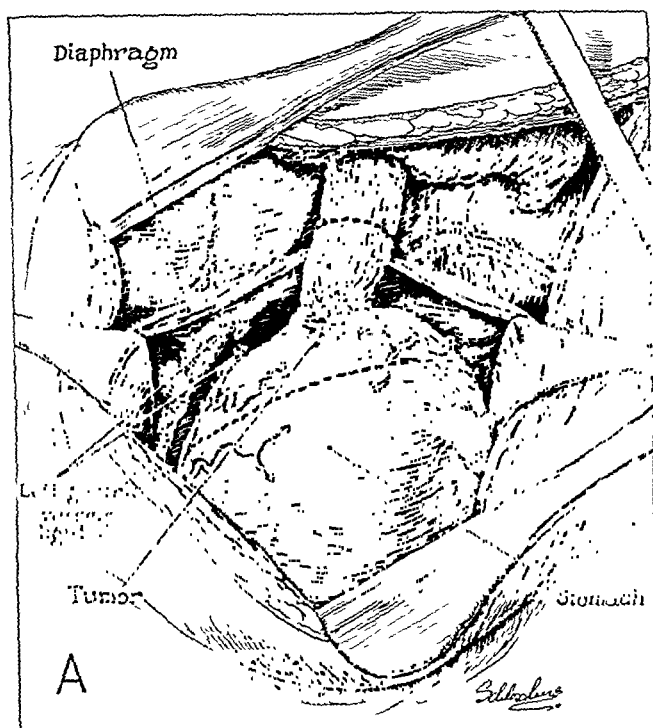


Fig. 2.—*A*, the tumor is exposed and the stomach drawn into the chest; the lines indicate the site of reaction. *B*, the tumor has been resected together with the adjacent portions of the stomach and the esophagus; the stomach is closed with interrupted silk sutures, and the esophagus is implanted into the stomach.

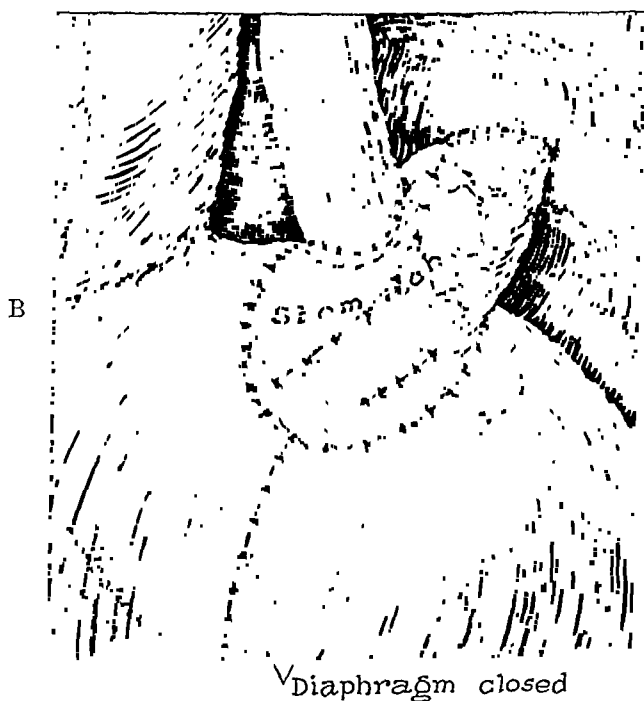
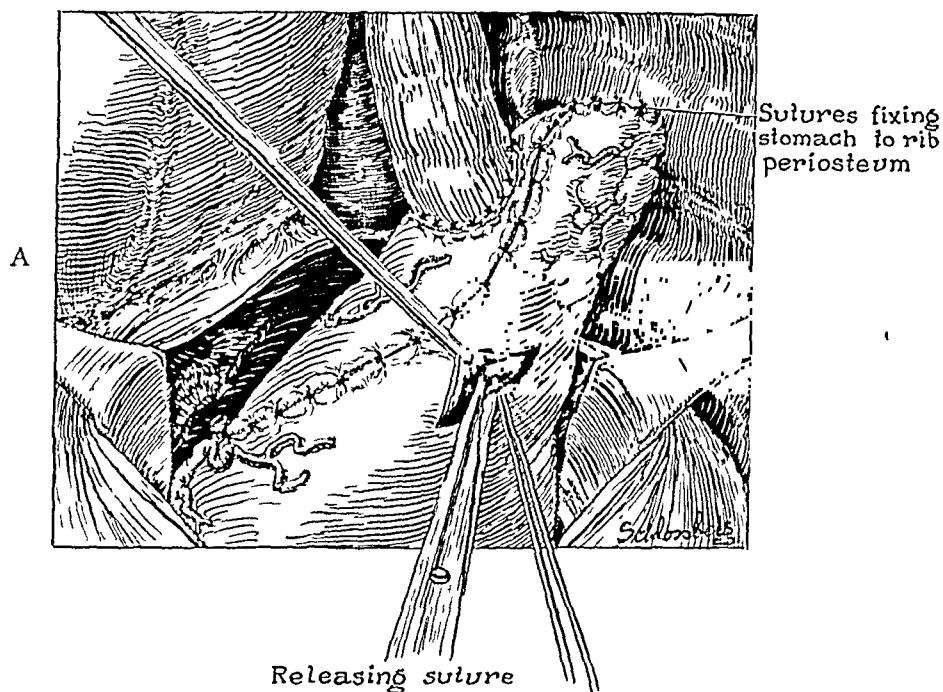


Fig. 3.—*A*, anastomosis with interrupted mattress sutures has been completed, and the lower end of the esophagus has been opened. *B*, the operation is completed; note the sutures fixing the stomach to the rib in order to avoid tension.

two layers of mattress sutures of medium silk. When this had been completed, the catgut ligature was cut in order to allow the esophagus to discharge freely into the stomach. The lower gastric wound was closed with interrupted silk sutures. The diaphragm was sutured snugly about the midportion of the stomach, leaving a conic segment of the stomach within the thorax. This portion of the stomach was then anchored to the costal periosteum in order to relieve the suture line of any tension.

A mushroom catheter was placed in the costophrenic angle at the ninth interspace, and after 8 Gm. of powdered sulfanilamide had been dusted into the field, the chest wall was closed in layers with silk. A small Kader-Senn gastrostomy was finally done. During the operation the patient received 1,000 cc. of citrated blood, 1,500 cc. of 5 per cent dilution dextrose in physiologic solution of sodium chloride and 250 cc. of human plasma. At the end of the procedure he was in good condition.

Sodium sulfathiazole was given intravenously for four days after operation, and a blood concentration of 4 to 9 mg. per hundred cubic centimeters was maintained. Feedings by gastrostomy tube were commenced on the fourth day, and thereafter sulfathiazole also was given by this route. Adequate fluid intake was maintained by the intravenous route. On the third night after operation the temperature rose to 101 F., but thereafter the patient was afebrile. The esophageal tube was removed on the seventh day, and fluid by mouth was first allowed on the eleventh day. On the fourteenth day thoracentesis yielded 550 cc. of blood-tinged fluid, which was sterile on culture. On the twenty-sixth day a roentgenogram made after a barium sulfate meal showed a wide well functioning stoma between the esophagus and the stomach. The wound healed by first intention and the patient was discharged on May 31 with the gastrostomy tube still in place. The pathologic diagnosis was adenocarcinoma extending into the esophagus and to two of the regional lymph nodes.

The patient returned one month later with definite empyema low on the left side of the chest. A short segment of the ninth rib was resected; the empyemic cavity was drained (*Bacillus coli*), and the patient was discharged after removal of the gastrostomy tube. When last heard from, four months after operation, he was eating all kinds of food, had gained 12 pounds (5.4 Kg.) and was doing light work.

COMMENT

The management in the case reported proved essentially satisfactory, and there seems little reason to alter it in the future. After open anastomosis with obvious contamination of the pleural cavity, the occurrence of small empyema is not surprising, although the use of sulfathiazole might provide better protection in another case. Postoperative strictures reported by other surgeons have manifested themselves within the first few weeks, whereas in the present case there was no evidence of stricture after four months and it thus seems unlikely that stricture will develop. During the first few months after operation, the gastrostomy must be kept open (although not used for feeding) in order to provide for retrograde dilation should this become necessary.

REVIEW OF UROLOGIC SURGERY

ALBERT J. SCHOLL, M.D.
LOS ANGELES

FRANK HINMAN, M.D.
SAN FRANCISCO

ALEXANDER VON LICHTENBERG, M.D.
MEXICO, MEXICO

ALEXANDER B. HEPLER, M.D.
SEATTLE

ROBERT GUTIERREZ, M.D.
NEW YORK

GERSHOM J. THOMPSON, M.D.
AND

JAMES T. PRIESTLEY, M.D.
ROCHESTER, MINN.

EGON WILDBOLZ, M.D.
BERNE, SWITZERLAND

AND
VINCENT J. O'CONOR, M.D.
CHICAGO

(Concluded from page 397)

URETER

Tumor.—Olovson²⁴ reports benign ureteral tumor in a woman aged 43 years who had pain for two years in the left side of the abdomen. This pain extended into the left renal region. On cystoscopy, a papillomatous growth was seen moving rhythmically in and out of the left ureteral orifice. A ureterogram revealed stenosis of the lower part of the ureter with a filling defect above. The ureteral growth, a benign papilloma, was removed transvesically.

Olovson states that 42 cases of benign ureteral tumor, mostly papilloma, have been reported. The growth is often located in the lower third of the ureter. The chief symptoms are hematuria, pain and a palpable kidney. Hematuria occurs in about 70 per cent of the cases. The filling defect in the ureterogram is a characteristic feature of ureteral tumor, but there is no typical picture suggesting the benign tumor. In the cases of benign ureteral tumor reported in the literature, two operative methods have been found expedient, namely, (1) local

24. Olovson, T.: Gutartige Harnleitergeschwülste, Acta chir. Scandinav. 84: 469-478, 1941.

treatment by cauterization and ureteral resection and (2) complete nephroureterectomy. The latter method has been employed in the majority of cases. In Olovson's opinion, the local procedure is the ideal method of treatment for benign ureteral tumor.

Stang and Hertzog²⁵ report 4 cases of primary carcinoma of the ureter. The average age of the patients was 58.2 years. The chief complaints were hematuria and pain in the lower portion of the abdomen. A tumor protruding from the ureteral orifice was noted in 3 of the cases. Ureterograms revealed dilated ureters at the site of the tumor and above the growth. Three of the patients died of metastasis after operation. The fourth is living and well at the age of 75 years, four and a half years after removal of the tumor.

Lazarus²⁶ states that metastatic tumor of the ureter is extremely rare. Only 18 cases are recorded in the literature, including 1 which he presents. In these cases, 7 tumors originated in the prostate gland, 2 in the bladder, 2 in the cervix, 1 in the urethra, 1 in the stomach, 1 in the bronchus and 2 in the breast. In 1 case, the primary focus was Hodgkin's disease. In Lazarus' case, the primary source was the ovary, which, on microscopic examination, presented malignant changes in a dermoid cyst. The right ureter only was involved in 7 cases, only the left in 5 and both ureters in 6. Metastatic tumor of the ureter must be differentiated sharply from primary tumor and from tumor invading the ureteral wall by direct extension. Such differentiation can only be made histologically by finding tumor cells in the perivascular lymph spaces or within the vessels of the ureter.

Randall²⁷ reports endometrioma of the ureter in the case of a woman aged 37 years. The patient's illness began a year before the initial examination with a sense of discomfort in the right loin. Immediately prior to examination she had a severe attack of pain in the loin associated with hematuria. Cyclic bleeding was not observed. Menses usually had been regular at thirty day intervals, but in the past year the menstrual intervals had lessened. She always had some pain during and shortly after each period. Urinalysis gave negative results except for a few leukocytes and cells in the blood. Urographic studies revealed a normal left upper renal tract; on the right side, some haziness was present in the shadow of the renal pelvis. In the upper half of the right ureter there were multiple defects, and in the lower half there

25. Stang, H. M., and Hertzog, A. J.: Primary Carcinoma of the Ureter: A Report of Four Cases, *J. Urol.* **45**:519-526 (April) 1941.

26. Lazarus, J. A.: Metastatic Ureteral Obstruction Following Carcinoma of the Ovary: Report of an Unusual Case of Pyonephrosis Resulting from a Metastatic Carcinoma of the Ureter, *J. Urol.* **45**:527-535 (April) 1941.

27. Randall, A.: Endometrioma of the Ureter, *J. Urol.* **46**:419-422 (Sept.) 1941.

was a definite rounded filling defect around which the contrast medium flowed. At cystoscopy, a catheter was passed to the right renal pelvis, and a pyelogram was made; this resulted in the diagnosis of a growth at the lower end of the right ureter. The ureter was exposed surgically, and a fusiform swelling was found in the lower end. The ureter then was freed from the bladder and the kidney and ureter removed through a second incision. The microscopic diagnosis was endometrioma.

Stone.—Spence²⁸ reviews 24 cases of stone at the ureteropelvic junction. In 23 of the 24 cases, urography revealed functional or anatomic damage to the kidney resulting from stone. Except for diagnostic purposes, the use of cystoscopic procedures is ill advised in cases of this type. This is strikingly brought out in the synopsis of 3 cases in which death occurred. Early surgical removal of stone at the ureteropelvic junction is the treatment of choice.

Osterbye²⁹ reports 113 cases of ureteral calculus. Ureteral stone occurred most frequently in men between the ages of 20 and 25 years and was usually unilateral. In 90 per cent of the cases, the urine was sterile; gross hematuria occurred in 30 per cent, and hematuria was evident microscopically in 95 per cent. In about half the cases, stone was locked just above the bladder. In 70 per cent of cases, stone will be passed naturally. Osterbye expresses the belief that instrumental treatment should be resorted to without giving expedient treatment a chance. Ureterolithotomy was performed in only 8 of the 113 cases.

Moring³⁰ reports 140 cases of ureteral stone. He considers chiefly ureteral manipulation and removal of stone. These methods were used in 98 cases (70 per cent); in 41 of these there were almost immediate results. The stone passed naturally in 21 per cent of the cases. Most of the patients had symptoms for only a short time. In 12 cases (9 per cent) some type of surgical procedure was carried out; 6 of the patients were operated on primarily, and the other 6 after cystoscopic methods had failed to bring down the stone.

Moring advises the transurethral method, as there is little risk and less loss of time. Forty-two patients were sent home with the expectation that the stone would be passed. They were followed for six months to five years, and in practically all cases the stone was passed. In most cases the patient did not know that the stone was being passed. Hydronephrosis developed in only a small number of the cases.

28. Spence, H. M.: Stones at the Ureteropelvic Junction, *J. Urol.* **45**:579-586 (April) 1941.

29. Osterbye, K.: Disease of Ureters and Its Treatment, *Ugesk. f. læger* **102**: 1189-1194 (Nov. 14) 1940.

30. Moring, S.: Treatment of Ureteral Calculi, *Ugesk. f. læger* **102**:1194-1197 (Nov. 14) 1940.

Ureterostomy.—Folsom and O'Brien³¹ report 12 cases of cutaneous ureterostomy. This is a simple operation and is well tolerated, even by patients already debilitated from advanced carcinoma. Cutaneous ureterostomy gives satisfactory renal drainage. At present, this seems to be the most practical way of diverting the urine when the ureters are badly damaged by dilatation from obstruction. The authors were impressed by the lack of difficulty experienced by the patients in keeping dry and comfortable.

Ureterocele.—Campbell³² states that ureterocele is a congenital obstructive lesion in which secondary urinary infection is the important complication. Resulting persistent pyuria, too commonly designated chronic pyelitis, is the symptom which almost always prompts the urologic diagnostic investigation.

Ureterocele is not unusual. It is notable that failure to identify ureterocele in young patients sometimes accounts for premature death. For this reason, the true incidence of the condition is doubtlessly less among adults than among the young.

The clinical picture is almost always that of chronic pyelitis; urinary back pressure pain may be a prominent symptom.

The diagnosis is readily made by urologic examination. Urography is frequently helpful, especially when ureterocele produces a cystographic filling defect.

Removal of the obstruction is the immediate treatment. Eradication of urinary infection, calculi or other complicating lesions is the essential accessory treatment.

BLADDER

Carcinoma.—Paterson³³ discusses roentgen therapy of cancer of the bladder. He states that tumor of the bladder, like tumor in the cervix, the mouth and the skin, can be successfully treated with roentgen rays. He also remarks that this method of treatment is not being used extensively at present, because the limited material does not permit the working out of satisfactory methods of treatment.

Paterson classifies tumor of the bladder from a roentgenologic and therapeutic point of view into three groups: (1) benign papilloma, (2) noninfiltrating cancer and (3) infiltrating cancer. In his cases, this diagnosis was based on contrast cystography and relief pneumocystography.

It is Paterson's opinion that satisfactory roentgen therapy is preferred to surgical operation in all cases, even as a first treatment. He

31. Folsom, A. I., and O'Brien, H. A.: Cutaneous Ureterostomy: A Report of Twelve Cases, *J. Urol.* **45**:587-597 (April) 1941.

32. Campbell, M. F.: Ureterocele, *J. Urol.* **45**:598-611 (April) 1941.

33. Paterson, R.: Cancer of the Bladder, *Brit. J. Radiol.* **14**:219-234 (July) 1941.

describes implantations of radium and condemns the cystoscopic implantation of radon seeds. He discusses the value of roentgen ray single exposure treatment by contact treatment, such as that recently described by Crane and others. This method to be successful requires the use of high doses, small fields and special methods of beam direction.

Cope³⁴ states that papilloma of the bladder may remain latent for long periods. Painless hematuria, although a common symptom, is by no means the only symptom for which patients seek advice. Retention of urine, frequency of urination, pain on urination or the passage of a piece of growth may cause the patient to consult the physician. Papilloma of the bladder has a great tendency to become malignant. Every patient who has been treated for papilloma of the bladder should be told of this danger in order to insure that he will report regularly for inspection of the bladder. Patients who have carcinoma of the bladder and to whom life has become unbearable from pain and frequency of urination should be given the chance of relief by transplanting the ureters into the rectum.

Hyams and Silberblatt³⁵ state that hemangioma occurs with relative frequency, not only on the skin or in different regions of the body, such as the liver, the gastrointestinal tract and the muscles, but also in the urinary bladder. It is considered the rarest of all tumors of the bladder.

The authors report a case of hemangioma associated with papillary carcinoma of the urinary bladder. The patient was a man aged 62 years. On cystoscopy, a sessile growth with coarse villi about 2.5 cm. in diameter was found on the right superior wall of the bladder. In the posterior base, a second and entirely different microscopic growth was seen; this was sessile, bluish and slightly elevated. Later, the bladder was opened, and both tumors were removed. One was definite papillary carcinoma and the other hemangioma.

Priestley³⁶ states that treatment of carcinoma of the bladder is a controversial subject and undoubtedly will be disputed for some time. Important factors which must be considered in selecting the proper form of treatment in each case of carcinoma of the bladder include the type, the grade, the extent and the site of the lesion, whether it is multiple or single, whether one or both ureterovesical orifices are

34. Cope, V. Z.: Concerning Papillomata of the Bladder, *Brit. J. Urol.* **13**: 74-82 (June) 1941.

35. Hyams, J. A., and Silberblatt, J. M.: A Case of Hemangioma Coincident with Papillary Carcinoma in the Urinary Bladder, *J. Urol.* **46**:271-277 (Aug.) 1941.

36. Priestley, J. T.: General Considerations in the Surgical Treatment of Carcinoma of the Bladder with Particular Reference to Total Cystectomy, *New York State J. Med.* **40**:1441-1445 (Oct. 1) 1940.

involved, the status of renal function, the presence or the absence of serious renal infection and the age and the general condition of the patient. When these various factors are considered, it must first be decided whether approach to the tumor should be transurethral or suprapubic. When this is decided, fulguration, electroexcision, implantation of radium, segmental resection or total cystectomy must be chosen.

In Priestley's opinion, roentgen therapy alone never constitutes the treatment of choice if a more direct attack can be made on the lesion. Until end results have been evaluated more accurately in relation to the various forms of treatment and the physical characteristics of the lesion itself, there will be no accurate information on which to base the proper choice of treatment.

It seems that total cystectomy might be employed to advantage more frequently, although the indications for total cystectomy cannot be stated dogmatically. In Priestley's opinion there are four main types of cases in which this operation might be considered—cases of (1) extensive low grade lesions, (2) low grade lesions of multicentric origin, (3) repeatedly recurring low grade lesions and (4) high grade lesions which, to the best of the physician's knowledge, have remained confined to the bladder. When total cystectomy is employed in these cases, the ultimate results should prove to be more satisfactory than they have been in the past.

Clancy³⁷ reports a neoplasm complicating diverticulum of the bladder in a man aged 83 years who had had complete retention of urine on several occasions. A cystogram revealed a large diverticulum on the right side of the bladder. The bladder was explored, and the fibrous ring connecting the bladder with the diverticulum was dilated. The patient died thirty days later. At necropsy it was found that the diverticulum contained papillary carcinoma.

Various authors have stated that neoplasms in diverticula of the bladder occur most frequently between the ages of 48 and 76 years. All authors seem to agree that hematuria is the outstanding symptom. The duration of symptoms varied from ten days to three years. The cystoscope and the cystogram are essential aids in making diagnosis. In cases in which carcinoma protrudes into the orifice of the diverticulum, the diagnosis is simplified. When it is possible to introduce the cystoscope into the diverticulum, much uncertainty is eliminated.

Collings and Welebir³⁸ report a case of osteoma of the bladder in a woman aged 67 years. Six years earlier, she had been treated with radium for carcinoma of the cervix vesicae. Roentgenograms of the

37. Clancy, F. J.: Neoplasm Complicating Diverticulum of the Bladder, *J. Urol.* **46**:486-490 (Sept.) 1941.

38. Collings, C. W., and Welebir, F.: Osteoma of the Bladder, *J. Urol.* **46**: 494-498 (Sept.) 1941.

bladder revealed several large round calcified bodies in the region of the bladder suggestive of calcified fibroids. Cystoscopy revealed a tumor mass 3 cm. in diameter in the region of the left ureteral orifice. Several smaller similar masses were found on the floor of the bladder. Through a suprapubic incision, a number of masses were removed from the mucosa of the bladder. These masses were bony; the largest was embedded in the mucosa. Microscopic examination revealed that the tumors were granulomatous. Sections through the tissue disclosed an acellular structure with the outlines of dense bony material. The diagnosis was probable osteoma of the bladder.

McDonald, Doss and Thompson³⁹ report their study of a group of neoplasms in which, histologically, some portions were suggestive of sarcoma and others were suggestive of carcinoma. It was possible to demonstrate the epithelial origin of the tumor in each of the 9 cases and to disclose that the carcinoma cells assumed characteristics which, if examined histologically, are diagnostic of sarcoma. The short clinical history and the poor results following treatment in these cases attest to the extremely malignant nature of all lesions of this type in the urinary bladder.

Kahle, Vickery and Maltry⁴⁰ discuss 2 cases of endometriosis of the bladder. In the first case, the mucosa was not involved, hematuria was not present, and endometrial infiltration was discovered in the course of a gynecologic operation. For this reason attention was not directed to the vesical involvement before operation, and cystoscopy was not carried out. This case is one of the few on record in which pelvic operation did not precede development of the endometriosis of the bladder.

In the second case, in which there had been a previous gynecologic operation, the vesical mucosa was involved, and hematuria had been present at intervals for six years. This case is unusual in that vesico-sigmoid fistula developed, although it is not possible to say whether it followed the apparently superficial injury of the sigmoid at the first operation or was the result of the endometrial process.

Cystectomy.—Vest and Curd⁴¹ report the case of a patient with infiltrating epidermoid carcinoma of the bladder which involved the vaginal vault and the uterine cervix. Total cystectomy with panhysterectomy was performed.

39. McDonald, J. R.; Doss, A. K., and Thompson, G. J.: Carcinoma of the Urinary Bladder Imitating Sarcoma, *J. Urol.* **46**:38-51 (July) 1941.

40. Kahle, P. J.; Vickery, G. W., and Maltry, E.: Endometriosis of the Urinary Bladder: Report of Two Additional Cases, *J. Urol.* **46**:52-56 (July) 1941.

41. Vest, S. A., and Curd, H. H.: Total Cystectomy Combined with Panhysterectomy, *Surg., Gynec. & Obst.* **73**:517-519 (Oct.) 1941.

Urograms revealed that the right kidney was functionless owing to obstruction and hydronephrosis on the left. Preliminary left nephrostomy was followed by relief of symptoms of the bladder and improvement in the patient's general condition. When laparotomy was carried out, evidences of metastasis or involvement of the lymph nodes were absent, but induration of the tumor extended into the region of the cervix and the vaginal vaults.

It was therefore decided to perform panhysterectomy in addition to total cystectomy. This operation was facilitated by ligation of the anterior branch of the internal iliac arteries on both sides. Vest emphasizes the importance of this step in a combined operation of this type.

The patient has learned to care for the nephrostomy tube and fifteen months after operation has shown no evidences of recurrence.

Hyperplastic Lesions.—Stirling and Ash⁴² report 22 cases of hyperplastic lesions of the urinary tract. Hematuria, dysuria or frequency of urination was found in every instance and was usually severe. The genesis of glands and cysts and their relation to carcinoma are discussed. Three patients had concomitant cysts and carcinoma of the bladder.

Brunn's follicle is an invagination or an extension of surface epithelium, and its subsequent fate depends on whether epithelial metaplasia progresses to a squamous or a glandular type. Follicular cystitis is a nonspecific entity, common in any chronic infection. Several hyperplastic forms of cystitis may be found in the bladder at the same time.

Stirling and Ash describe for the first time a lesion termed "papillary hyperplasia." It may combine one or more features of the other types, and it is important, since it may simulate tumor.

Lesions of the Nerves.—Hinman,⁴³ in considering care of the bladder at the front when paralyzed by injuries to the spinal cord, states that the patient is wholly at the mercy of those about him. The initial effect of an injury of the spinal cord, if any, on micturition is the same, no matter at what level of the cord injury occurs. Spinal shock causes muscular atony. The period of urinary disability, however, which is manifested by retention and overflow incontinence, may last only a few days or may persist for many months, depending on the location and the severity of the injury. Recovery from this initial effect likewise is variable with the site and the extent of the lesion. The two effects of injury to the spinal cord are (1) the initial effect of retention and

42. Stirling, W. C., and Ash, J. E.: A Clinicopathologic Discussion of Hyperplastic Lesions of the Urinary Tract, *South. M. J.* **34**:358-364 (April) 1941.

43. Hinman, F.: The Care of the Bladder at the Front When Paralyzed by Injuries to the Spinal Cord, *J. Urol.* **46**:499-504 (Sept.) 1941.

overflow incontinence and (2) the variability in the time and the type of recovery; these necessitate two periods of management for these patients. Only one period of management is required for patients with temporary acute retention, while two are necessary for those with a bladder affected by a permanent neurogenic condition. In the first period, management is concerned with initial retention and overflow incontinence common to both groups and the second with the changing types of dysfunction occurring in a certain order, according to which one of the three levels of innervation have been injured and the extent of this injury. The management of retention in the two groups of cases is different.

The method of noninterference, which allows distention and overflow, is a form of neglect occasionally justified by circumstances. It should be attempted only as a temporary expedient when opportunity and facilities for proper care are wanting. It may be the least injurious form of treatment under these circumstances and for the short period which will be required for the patient to reach the place where proper methods can be used. It is an emergency measure and never to be used for long periods. Rarely does an uninfected bladder thus neglected rupture and rarely are distention and overflow incontinence painful to the paralyzed patient. When urinary infection is present, prolongation of distention is extremely dangerous.

The method of manual expression of urine is best for the early attainment of an automatic bladder and, when it works, may save many months of treatment with catheters. It is likewise a method which avoids urinary infection better than any other.

The use of a retention catheter with continuous tidal irrigation has what may seem to be slight advantages over the use of a simple retention catheter or intermittent catheterization. Experience has proved, however, that the prevention of overdistention of the bladder by continuous drainage and reduction of infection by automatic irrigation are advantages not to be had by other methods. Further, the use of a retention catheter with tidal irrigation hastens development of an automatic bladder.

The method of suprapubic cystostomy and continuous tube drainage for the acute initial retention caused by injury to the spinal cord is difficult to appraise. It would seem radical to advise its routine use at the onset of acute retention, but often it is indicated later when manual expression fails, when a urethral catheter will not be tolerated, when virulent urethritis, acute prostatitis, epididymitis or ascending infection develops or when vesical hemorrhage is so severe that it cannot be controlled by the urethral catheter. Hinman states that a safe rule to follow is to insert a suprapubic tube immediately if the injury is severe, no matter what its location, provided it will be days

or weeks before the patient reaches the place where faithful and technical management can be given him. A cystostomy catheter is less injurious than neglect of the many technical procedures required in the successful use of any of the other methods. The entire program of management of the period of acute retention is to prevent ascending urinary infection. Urinary drainage is one method of prevention, and aseptic urinary drainage is the best. Regular periodic manual expression, the use of a retention catheter and suprapubic cystostomy are the only methods for securing continuous drainage with the least risk of pyelonephritis. In civil practice, the method of noncatheterization and manual expression is preferred. If this fails or if infection appears, use of a retention catheter with continuous tidal irrigation is indicated. When this method becomes contraindicated for any of the many reasons mentioned earlier, suprapubic cystotomy is performed. In military practice, however, this order of preference must be reversed, for the sole reason that technical performance of the first two methods is unattainable at the front or evacuation centers. The delay of even a few days to reach a hospital will be too late. A simple suprapubic kit should be part of the surgeon's emergency outfit, and suprapubic cystotomy should be performed at the earliest opportunity for acute retention caused by injury to the spinal cord.

Rudy and Muellner⁴⁴ state that neurologic disturbance of the urinary bladder is common in cases of diabetes mellitus. It should be looked for during exacerbation of diabetes among patients with diabetes who have urinary symptoms, who are receiving deficient diets and who have lost much weight. Disturbances of the bladder are frequently associated with other abnormal neurologic signs and symptoms. For properly treated patients, the prognosis is fair.

Treatment should consist of control of the diabetes and administration of a diet which is as nearly normal as possible and is high in vitamins and minerals. Vitamin concentrates, especially vitamin B₁ (thiamine) and those of the B complex, should be used extensively and for prolonged periods. Bladder instrumentation should be avoided in cases in which infection is absent. Constant drainage of the bladder, chemotherapy and urinary antiseptics are of value when infection of the urinary tract is present.

Robinson⁴⁵ states that the correct handling of the bladder in cases of injury to the spinal cord is of paramount importance at present. It is obvious that treatment can be based only on a sound appreciation of

44. Rudy, A., and Muellner, S. R.: The Neurogenic Bladder in Diabetes Mellitus: Early Recognition and Treatment with a Report of Cases, *J. Urol.* **45**: 844-857 (June) 1941.

45. Robinson, R. H. O. B.: The Treatment of the Bladder Following Injury to the Spinal Cord, *Brit. J. Urol.* **12**:244-248 (Dec.) 1940.

the normal physiology of micturition, so far as this is known, and of the changes that result in the function of the bladder after damage to the cord. After damage to the cord the condition of spinal shock occurs and interferes with the activity of the segmental reflex below the level of the lesion. The effect is greatest in the segments nearest the site of injury and least in those most remote. The duration is variable, and relapse is possible. During the presence of spinal shock, activity of the bladder is interfered with from suppression of the reflex arc; the effect is greatest if the site of injury to the cord is low. Destructive lesions of the sacral segments or of the cauda equina denervate the bladder and reduce it to the autonomous state; as a result, it undergoes hypertrophy; its capacity diminishes, and voluntary control is lost permanently. Anatomic division above the sacral segments cuts off all cortical inhibition, so that emptying cannot be controlled and will take place as soon as the wall of the bladder is stretched sufficiently. Such a bladder is spoken of as the uninhibited reflex type and is the best end result that can be expected after complete section of the cord. Intercurrent infection may cause spinal shock to recur at any time and may result in the bladder regressing to a state of flaccid atony.

After injury to the cord at any level, the bladder must pass through certain definite stages on its road to recovery; the stage reached depends on the site of the lesion. The progress to recovery can be divided into five stages, namely, (1) the atonic, (2) the autonomous, (3) the hyper-tonic, (4) the uninhibited reflex and (5) the normal cord bladder. Any actual stage is determined according to four criteria: (1) tonus of the detrusor urinae muscle; (2) optimal storage capacity, together with the presence or the absence of emptying contractions; (3) the amount of residual urine expressed as a percentage of the fill and (4) reflex activity of the external sphincter.

In treatment, the principle of tidal drainage introduced by Munro appears to produce results far superior to anything achieved previously. A siphon and an irrigating apparatus are attached to an indwelling catheter, which periodically fills and empties the bladder to an extent and at a rate corresponding to normal, until activity of the bladder is regained. By this method, reduction of urinary sepsis from 72 to 14 per cent is claimed in cases of injuries to the spinal cord. The disastrous effects of overdistention of the bladder with infected urine are prevented, as well as the later development of a contracted bladder. The apparatus for tidal drainage must be checked from time to time with regard to the volume of fluid entering the bladder and the head of pressure forcing it in so that it can be made to correspond with the progressive stages of recovery. The indwelling catheter should be changed once a week. For men it should be of the whistle tip type. An ordinary self-retaining catheter is adequate for women. Rubber

catheters should be used for both sexes. The whole apparatus should be cleaned once a week. If the bladder is foul, the catheter will need to be cleaned by manual irrigation at intervals until clean enough to avoid intermittent blockade during tidal drainage. In view of Munro's results, it appears imperative to try his methods whenever possible.

Scott⁴⁶ states that proper care of the paralyzed bladder is an important part of the management of patients with traumatic myelitis. Early suprapubic cystotomy answers the question of adequate drainage and urinary asepsis more satisfactorily than any other procedure, particularly in the early stages; often it may be the most satisfactory procedure as a permanent method of bladder drainage. The tendency of the paralyzed patient toward the formation of renal calculi should always be kept in mind in these cases.

Rupture.—Beresford-Jones⁴⁷ reports a case of spontaneous intraperitoneal rupture of the urinary bladder. The patient was a woman aged 27 years with a sudden pain in the abdomen while walking. The abdomen became distended, and free fluid was found in the peritoneal cavity. Thirty-eight fluidounces (1.1 liters) of urine was withdrawn by catheter. Owing to the fact that catheterization gave positive results on several occasions, the diagnosis of rupture of the bladder was not made. The patient died forty hours after the attack. At necropsy, the abdomen was found to contain 2 pints (1,000 cc.) of fluid. Considerable inflammatory changes were seen on the surface of the intestine. Examination of the bladder disclosed an intraperitoneal rupture on the posterior side.

Inversion.—Micheletti⁴⁸ describes an unusual case of total inversion of the bladder, one of the gravest accidents that can befall this organ. Only 14 cases have been found in the literature of the last fifteen years; in 5 of these, inversion was through the urethra and in 9, through a fistula. In Micheletti's case, inversion was through a fistula.

The patient was a woman 68 years of age who at the age of 40 years had suffered vesicovaginal fistula at the time of a severe labor complicated by a third degree laceration of the perineum. She had refused surgical repair for both conditions. Examination revealed a large vesicovaginal fistula, total prolapse of the uterus and the vaginal wall, marked posterior enterocele and partial prolapse of the rectum. Two operative interventions were carried out. The first consisted of repair of the fistula with temporary reduction of the uterine prolapse;

46. Scott, R. T.: Care of Paralyzed Bladder Secondary to Spinal Fractures, *Northwest Med.* **40**:336-338 (Sept.) 1941.

47. Beresford-Jones, A. B.: A Case of Spontaneous Intraperitoneal Rupture of the Urinary Bladder, *Brit. J. Surg.* **29**:154-156 (July) 1941.

48. Micheletti, G.: Inversione totale della vescica (contributo patogenetico e clinico), *Policlinico (sez. chir.)* **47**:481-490 (Dec.) 1940.

the second, performed a month after the first, accomplished restoration of the perineum. The results of both procedures were excellent.

The particular interest in this case lies in the unusual sequence of the evolution of the lesions, which was cystocele, rectocele, prolapse of the uterus and, finally, posterior enterocele. The patient's history revealed that incontinence of urine had developed one week after trauma; prolapse of the rectum appeared two months later. After twelve years the uterus prolapsed; thirteen years after this there was partial prolapse of the bladder, which reached the state of complete inversion three years later, or twenty-eight years after the original injury.

In observations made on the mechanism of inversion of the bladder it is worthy of note that the part first involved in the process was either the anterosuperior or the posterosuperior wall and that the last portion of the organ to be exteriorized was the trigone, which suffered inversion much more rarely than the other portions. In Micheletti's case, however, the order of the developments was determined by the twofold circumstance of the serious perineal laceration and the fistula located on Pawlik's triangle, a location so close to the ureteral orifices that the pressure which normally would be exerted by the bladder on the anterior wall of the vagina was markedly reduced. As a result, the weakest point was the posterior vaginal wall; this caused prolapse of the uterus to begin with rectocele at a time when the loss of fat and senile atrophy associated with the menopause had upset the already labile equilibrium between the resistance of the pelvic floor and the intra-abdominal pressure. That inversion had begun with extrusion of the trigone was revealed by the absence of symptoms of urinary retention and the constant presence of two ureteral protuberances which protruded from the fistula.

The mechanism of the formation of this inversion may be likened to that of hernia. The traction of the genital prolapse caused the natural connections of the trigone and the uppermost parts of the vagina to relax. They did this the more easily in view of the presence of the large vesicovaginal defect. After the descent of the vaginal wall, the posterior part of the trigone, having lost its natural adhesions, found an artificial opening, into which it readily engaged. Then, as the traction grew stronger, the supporting apparatus of the bladder became reduced to its lowest terms, until a sudden diminution of abdominal pressure caused the partial inversion to become total.

The complete recovery in this case was the more remarkable in view of the age of the patient and the presence of serious unilateral pyonephrosis. The case is of interest in that it serves to define more precisely the etiology and pathogenesis as well as the clinical picture of inversion of the bladder.

Contraction of Neck of Bladder.—Dillon,⁴⁹ in discussing contracted neck of the bladder, states that hyperplasia of the prostate is apparently prevented by early infection and replacement by fibrosis of the sub-mucous prostatic glands. Fibrous ring contractures of the neck of the bladder with hypertrophy of the interureteric ridge follow infection in young adults. Diagnosis is based on nocturia and the degree of angulation of the floor of the bladder with the prostatic urethra as determined by a panendoscope. The presence of trabeculation and hypertrophy of the interureteric ridge with a deep retrigonal pouch is another aid to diagnosis. Best results are obtained by cold steel cutting and light coagulation of the bleeding points. Strong blended tube and spark gap cutting is frequently followed by further fibrosis, which necessitates posterior dilations or further transurethral resection.

HYPOTHYROIDISM AND BLADDER FUNCTION

Sherrill and Mackay⁵⁰ discuss hypothyroidism and bladder function and report their findings in an experimental study. Atrophy of the bladder observed among patients with hypothyroidism stimulated their study of the relation of these conditions in the albino rat. Rats with hypothyroidism regularly revealed evidence of atony of the bladder; this was measured by the filled region, demonstrated by a radiopaque compound, in emptying time of the bladder and lowered ability to sustain an artificial increase in intrabladder pressure.

PROSTATE GLAND

Stone.—Gutierrez⁵¹ reports a series of 29 cases of prostatic calculi; in 17, operation was performed. In treating infection of the lower portion of the urinary tract, it should always be borne in mind that it is possible for calculi to be present within the prostate. Stone is much more common than has been believed, since it runs a symptomless course over a long period and tends to excite inflammation and obstruction slowly. Even when it is found accidentally, the patient should be closely observed because he is harboring latent infection which in the course of time may lead to irreparable damage to the gland, cause abscess, destroy function and, in cases in which the condition is advanced, lead to complete calcification.

Prostatic stone falls into three classes, namely, (1) endogenous, (2) exogenous and (3) endoexogenous, according to the way in which it

49. Dillon, J. R.: Contracted Bladder Neck, a Frequent Result of Youth Delinquency, *J. Urol.* **46**:510-513 (Sept.) 1941.

50. Sherrill, J. W., and Mackay, E. M.: Hypothyroidism and Bladder Function: An Experimental Study, *J. Urol.* **46**:34-37 (July) 1941.

51. Gutierrez, R.: Perineal Prostatotomy and Prostatectomy for the Removal of Prostatic Calculi, *Ann. Surg.* **113**:579-624 (April) 1941.

develops: (1) stone primarily within the substance of the prostate gland as a result of the slow deposit of calcium around the corpora amylacea found normally within the acini and the tubules; (2) stone forming within some part of the upper portion of the urinary tract, later becoming embedded within the region of the prostatic urethra; (3) stone originally forming within the prostate, later coming into contact with exogenous urinary deposits which accelerate the growth of stone so that it becomes prostatourinary calculus. All types may be present in the same case. For treatment, operative removal is demanded when symptoms are produced. At first, the symptoms are insidious and may appear as minor urinary, rectal or genital manifestations of an indefinite nature. As time goes on, they may range from mild frequency and dysuria to total hematuria and complete retention of urine. A few patients complain of urethral stricture. Arthritis or generalized sepsis of long standing was present in some of the cases in the author's series. The association of prostatic calculi with parenchymal prostatitis and adenomatous prostatic hypertrophy is a common occurrence.

Frequently, the diagnosis can be made by rectal palpation, which, in cases in which the condition is advanced, elicits characteristic crepitation and reveals the presence of hard nodules. The presence of these nodules can be confirmed by roentgenograms or urethrocystograms. Cystoscopic examination is helpful, especially if prostatic hypertrophy or characteristic bullous edema is present at the floor of the neck of the bladder and in the region of the prostatic urethra. In 67 per cent of the cases, the diagnosis was made by rectal palpation; roentgen examination was carried out in all cases. It should be emphasized that a urographic examination should not be considered complete that does not include the region of the prostate, since the discovery of clinically unsuspected prostatic calculi by roentgen examination is common.

When operation is indicated, the best surgical treatment appears to be perineal prostatolithotomy. When the condition is associated with adenomatous prostatic hypertrophy, perineal prostatectomy assures permanent cure. Not only should all prostatic stone be removed, but open drainage also should be maintained to relieve infection and restore good function if permanent cure is to be obtained. In 13 of the 17 cases in this series in which operation was performed, the patients were cured, and in 4, they were improved. Of 12 patients who were not operated on but who were treated medically and urologically, 5 were improved, and 7 were not. It appears that endoscopic prostatic resection is not applicable in the majority of these cases, since, as a rule, the stones are multiple. In cases in which prostatitis is a complicating factor, the stones are in closed infected pockets or lie near the capsule in cases of adenomatous prostatic hypertrophy.

Emmett⁵² considers the various methods now employed for removal of prostatic calculi, namely, suprapubic prostatectomy, perineal prostatolithotomy, transurethral removal of stone and subtotal perineal prostatectomy, an operation recently described by Henline. Under certain circumstances, each of these procedures seems to possess some advantage. It has been Emmett's experience, however, that the majority of prostatic calculi can be removed satisfactorily by means of transurethral measures. Stone too large to be removed through a cystoscope can be maneuvered into the bladder and crushed with a lithotrite. If, at times, a few fragments are permitted to remain, they usually do not cause symptoms. However, they can be removed at a second operation if desired.

Emmett presents 2 cases of prostatic lithiasis. In 1 of these, the patient was a man 73 years of age who had prostatic enlargement, grade 2. Virtually the entire prostate was filled with calcareous material which was satisfactorily removed by transurethral measures with the use of a McCarthy panendoscope and a Collings knife. The stones were dislodged, maneuvered into the bladder and subsequently crushed with a Bigelow lithotrite. The second case was similar to the first.

Carcinoma.—Because of the frequency of metastasis to the spinal column in malignant disease of the urogenital tract, particularly prostatic carcinoma, the observations of Wolfson, Reznick and Gunther⁵³ on the early diagnosis of metastasis to the spinal column may be of interest to urologists.

Early involvement of the vertebral bodies which is not demonstrable roentgenographically may be inferred by an increased sedimentation rate, elevated or rising values for serum phosphatase and the type of radicular pain.

This root pain is almost always sharply defined and limited to definite dermatomes, or regions supplied by the nerve roots adjacent to the vertebra or vertebrae involved. It may be confused with the root pain of arthritis; however, there are a number of distinct differences (table). The triad of accelerated erythrocyte sedimentation rate, increase in the level of serum phosphatase and sharply defined regions of spinal nerve root pain is presumptive evidence of malignant metastasis to the spinal column, even in the absence of positive

52. Emmett, J. L.: Transurethral Removal of Large Prostatic Calculi, Proc. Staff Meet., Mayo Clin. **16**:289-293 (May 7) 1941.

53. Wolfson, S. A.; Reznick, S., and Gunther, L.: Early Diagnosis of Malignant Metastases to the Spine: A Clinical Syndrome, J. A. M. A. **116**:1044-1048 (March 15) 1941.

roentgen findings. It is important to recognize this early involvement of vertebrae because adequate roentgen therapy produces dramatic relief of pain and regression of the lesions.

Hyperprostate.—Draper, Slaughter and Denslow,⁵¹ in discussing the effect of testosterone propionate on benign prostatic hypertrophy, state that they did not observe any apparent improvement in the urinary status of their patients which could not be duplicated by the injection of sterile solution of sodium chloride.

Wilhelmi⁵⁵ states that most urologists agree that resection is the method of choice in the treatment of all types of glandular obstruction except in cases of adenoma. The indwelling catheter should be omitted whenever possible and supplanted by intermittent catheterization or

Important Differential Findings in Spinal Metastasis and Spinal Osteoarthritis

	Spinal Metastasis	Spinal Osteoarthritis
Distribution of peripheral pain	Usually limited to narrow zones of one or two nerve roots' distribution	Usually covers a large number of spinal dermatomes, with wide areas of distribution
Periodicity and rhythmicity of pain	None; constantly present and intense; relief only by roentgen ray therapy	Influenced by meteorologic conditions; relief by analgesics, vitamin B ₁ and physical therapy
Effect of motion on the pain	Aggravates and intensifies the pain; patient shows reluctance to move once a relatively comfortable position is attained	Tends to relieve the pain; patient is constantly turning and changing position because motion affords relief
Deep percussion tenderness	Percussion tenderness over the suspected vertebrae is a constant sign	Percussion tenderness is not present; cutaneous sensitivity may be present
Sedimentation rate	Increased, usually greatly so	Not increased
Serum phosphatase	Increased, or increasing; above 4 Bodansky units	Not increased

suprapubic drainage. Whenever possible, cystoscopy should be followed by immediate operation. The levels of nonprotein nitrogen and urea nitrogen do not necessarily need to be within normal limits before operation if they are stabilized. Ligation of the vas deferens should be compulsory in cases in which the urine is infected and in those in which there is an old history of gonorrhea. Spinal anesthesia administered in small doses is the anesthesia of choice.

The hydrostatic gage is an important accessory in preventing rupture of the bladder or physiologic disturbances from intravesical overdistention. Careful postoperative asepsis with a closed system of

54. Draper, J. W.; Slaughter, G., and Denslow, C.: The Effect of Testosterone Propionate on Benign Prostatic Hypertrophy, *J. Urol.* **45**:539-547 (April) 1941.

55. Wilhelmi, O. J.: Refinements in Technique Imperative for Successful Transurethral Prostatectomy, *J. Urol.* **45**:612-621 (April) 1941.

drainage is advocated. Early removal of the indwelling catheter and close scrutiny during the follow-up are suggested.

Polse⁵⁶ states that caution should be exercised at all times in doing resection of the prostate. When a patient complains of sudden severe pain in the abdomen while under subarachnoid anesthesia or if extravescical suprapubic distention is suspected, it is advisable to make cystograms immediately. Intensity of the symptoms is usually dependent on the extent and the duration of the extravasation. The treatment for extraperitoneal extravasation is immediate drainage of the bladder and the prevesical space.

Milner and Engster⁵⁷ state that in their hands transurethral prostatic resection is the operation of choice in practically all cases of prostatic obstruction. Mortality and morbidity with the attendant economic distress are greatly reduced. Good results depend on resection of all the obstructing tissue and preferably down to the prostatic capsule. If tissue to which the blood supply has been destroyed remains, more marked cystitis with severer symptoms is certain to result after operation. All patients with incontinence should undergo cystoscopic examination, and any tissue impinging within the external sphincter should be resected.

Tuberculosis.—Strom and Thompson⁵⁸ report a case of primary tuberculosis of the prostate. They state that tuberculosis of the prostate is seldom recognized and that it is difficult to diagnose clinically. The patient was a man aged 30 years who complained of pain in the left upper quadrant of the abdomen. The urine was normal. He was operated on for cholecystitis with gallstones and died five days later. At necropsy, evidence of tuberculosis in the lungs or the hilar nodes was absent. The kidneys, the ureters and the bladder were grossly normal. A small abscess was found in the center of the left lateral lobe of the prostate. Microscopic evidence of tuberculosis in the lungs, the kidneys or the bladder was absent. The abscess in the prostate revealed the typical microscopic structures of tuberculosis. Tubercle bacilli were demonstrated in the stains, but there was no evidence of tuberculosis in any other part of the body. Strom and Thompson express the belief that this was a case of true primary prostatic tuberculosis of the genital tract.

56. Polse, M. L.: Extraperitoneal Rupture of the Bladder in Transurethral Prostatectomy, *J. Urol.* **46**:528-534 (Sept.) 1941.

57. Milner, W. A., and Engster, H. C.: Modern Methods of Handling Prostatic Obstruction: An Evaluation of Transurethral Resection Based on Seven Hundred Cases, *J. Urol.* **46**:278-282 (Aug.) 1941.

58. Strom, G. W., and Thompson, G. J.: Primary Tuberculosis of the Prostate: Report of a Case, *J. Urol.* **45**:858-862 (June) 1941.

TESTIS

Tumor.—There has been some speculation⁵⁹ as to the lytic properties of the serum of normal pregnant women for chorionic epithelium. It has been reasoned that in many respects the growth of the placenta resembles that of a malignant tumor, that the chorionic villi invade the uterine musculature and that emboli from this invasive tissue are carried to the lungs. Careful examination of the lungs of women who died in childbirth revealed that chorionic emboli were present in 80 per cent of those studied.

However, this invasive tissue fails to grow or produce metastatic tumors, and it is reasoned that there must be some substance in the serum of pregnant women and animals which inhibits this growth and which is lytic for trophoblastic cells and cell emboli. This substance keeps the balance and prevents the chorionic epithelium from running wild. On this basis, it has been suggested that the serum of normal pregnant women be used in the treatment of chorioepithelioma among both men and women.

Twombly and Hocker report the treatment with pregnancy serums of a patient who had chorioepithelioma of the testis with extensive metastasis. Careful urinary assays were made for chorionic gonadotropin, estrogens, androgens and pregnandiol during treatment. Before treatment, the urinary output of chorionic gonadotropin was high, as it usually is in cases of testicular chorioepithelioma; 40,000 to 130,000 mouse units was excreted daily. After the intravenous injection of 250 cc. of serum from the blood of parturient women on two occasions and on another of 250 cc. of serum from blood of the umbilical cord, the urinary output of chorionic gonadotropin increased to as much as 440,000 mouse units daily.

This was not caused by the hormone content of the injected serum, which at most contained only 2,000 to 4,000 mouse units; the observed increase in the urine was 300,000 mouse units. Twombly and Hocker conclude that the increase was caused by nonspecific protein shock.

Urinary estrogenic substances were increased over the values for normal men or menopausal women, and this explains the patient's gynecomastia. The androgenic output was normal, and a crystallized substance was extracted which was thought to be pregnandiol. The serum treatment combined with intensive roentgen therapy had no effect on the progress of the disease, and the patient died.

Epididymitis.—Smith⁶⁰ discusses infiltration of the spermatic cord with procaine hydrochloride as treatment for epididymitis. He follows

59. Twombly, G. H., and Hocker, A. F.: Chorioepithelioma in the Male: Treated with Pregnancy Serum, *Surg., Gynec. & Obst.* **73**:733-739 (Nov.) 1941.

60. Smith, D. R.: Treatment of Epididymitis by Infiltration of Spermatic Cord with Procaine Hydrochloride, *J. Urol.* **46**:74-76 (July) 1941.

the method of Imbert, who stated that the symptoms associated with acute epididymitis, namely, pain, swelling and redness, are largely caused by a neurovascular disorder and that block of the sympathetic nerves to the testis may relieve pain and bring about rapid cure. Since the sympathetic nerve fibers to the testis and epididymis accompany the vas deferens and the arteries to the testis, interruption of their impulses could easily be obtained by infiltration with procaine hydrochloride. Imbert injected a 1 per cent solution of procaine hydrochloride into the spermatic cord.

In 23 cases of acute epididymitis, the infection was gonorrheal in origin in 15. In most cases the pain was relieved within thirty hours, and the testicular swelling subsided within two weeks. In 8 cases of nonspecific epididymitis, pain disappeared in the majority of cases within twenty hours. The organs were reduced to normal size within about three days. When pain was not relieved within twenty-four hours, reinjection of the cord was carried out. Rarely was a third injection necessary.

During the first five months of 1940, Smith similarly treated 12 patients with acute epididymitis. Eight of these patients had epididymitis of gonorrheal origin. Two obtained complete and permanent relief of pain within seconds after the injection; 4 were relieved of pain within twenty-four hours, and 2 required reinjection the next day. The second injection was followed by complete relief of discomfort.

Three patients had nonspecific epididymitis. The pain of 2 was relieved within twenty-four hours after the injection. The other patient required reinjection twenty-four hours after the first infiltration. This discomfort disappeared forty-eight hours later. In 11 cases, resolution of swelling in the affected epididymis was hastened by this procedure.

Smith uses 10 to 20 cc. of a 1 per cent solution of procaine hydrochloride for infiltration. His technic is as follows: The spermatic cord is picked up with thumb and forefinger above the affected testis, while the overlying scrotal skin is held tense. A no. 22 needle is passed through the skin and, injection being maintained all the while, is advanced through the entire cord. The needle is then partially withdrawn, and by changing its angle in relation to the cord other regions are infiltrated in turn until the entire structure has been injected.

This procedure blocks all periarterial and perivascular sympathetic and sensory nerve fibers so that in a few seconds subjective numbness of the testis occurs, and the organ is painless to pressure. After one or two hours, the numbness of anesthesia disappears, but in cases in which the outlook is most favorable pain or tenderness does not recur. In others, mild degrees of discomfort may return and then disappear on the next day. If pain is still present after twenty-four hours, treatment should be repeated.

TORSION OF THE SPERMATIC CORD

Beare⁶¹ states that torsion of the spermatic cord is relatively common. This would be particularly true if the correct diagnosis were made in all cases. Without a doubt, many cases in which a diagnosis of acute epididymitis, orchitis or strangulated hernia is made are in reality cases of torsion.

It is likely that torsion cannot take place in a spermatic cord and testis which have had normal anatomic development in relation to the surrounding structures. Attachment of the vessels and the mesentery to the lower pole of the testis to form only a narrow band instead of the normally broad one may be a causative factor. The same is true of a large tunica vaginalis attached high on the cord, since this allows too great a range of motion of the testis. Exercise and exertion seem to be part of the immediate cause, but many cases have been reported in which torsion occurred during sleep or when the patient was not exercising.

The onset of pain in the testis is sudden and is soon followed by swelling. According to Cabot, if the patient is a young boy, a history of repeated attacks of testicular pain without urethritis or urinary infection is almost diagnostic of torsion of the cord. Vomiting, a mild degree of shock and elevation of temperature may or may not accompany the attack. The testicular mass will usually be high in the scrotum, and the epididymis will be anterior or lateral to the testis instead of in the normal posteromedial relation. Elevation of the testis will increase the discomfort. The condition occurs as often on the left as on the right side. There are two types, intravaginal and extravaginal, according to whether torsion occurs within or without the tunica vaginalis.

In the majority of cases the best treatment is open operation. If the testis and cord are found to be viable, it may be possible to untwist the cord and suture the testis and cord to the scrotal wall so that torsion cannot recur. If the testis and cord are necrotic, orchidectomy is the procedure of choice. Some physicians favor manual detorsion without opening the scrotum, but in most cases this is impossible, and valuable time is lost in the attempt. In cases of recurring torsion, if the twist is not severe enough to produce gangrene immediately, chances for preserving the testis are best. This is true also in cases of acute torsion, if the condition is recognized and operation is performed immediately.

61. Beare, J. B.: Torsion of the Spermatic Cord: Report of Case, Proc. Staff Meet., Mayo Clin. **16**:430-432 (July 2) 1941.

HYDROCELE OF THE CANAL OF NUCK

Counseller and Black⁶² state that hydrocele of the canal of Nuck is encountered only rarely. They report 17 cases.

Hydrocele or cystic tumor which accompanies the round ligaments through the inguinal canal of women is the exact counterpart of encysted hydrocele of the cord of males and results from the accumulation of fluid in a persisting diverticulum of Nuck, which corresponds to the vaginal process of the peritoneum in the male. In keeping with this concept of its origin, the cyst is usually found accompanying the round ligament but not originating within it. It is lined with a pavement epithelium similar in all respects to the cells lining the peritoneal cavity. The wall of the hydrocele is made up chiefly of fibrous tissue with a single layer of flattened cells on the inner surface. Smooth muscle may be present in the wall, but this finding is not constant. The most important problem presented by the condition is the differential diagnosis, chiefly from hernia. A careful history should serve to distinguish hydrocele from vulvovaginal cysts.

In the 17 cases from the Mayo Clinic, the differential diagnosis between hernia and hydrocele in female patients was difficult. In most cases, rather small tumors were so well confined to the inguinal canal that they could not be palpated readily. Many of the hydroceles were associated with hernia, and this complicated the questions of whether the mass could be reduced and whether there was an impulse on coughing. In some cases, the cysts were small enough to be freely movable and to be forced toward the subcutaneous inguinal ring when the patient stood or strained. In virtually all such cases the findings indicated to the examiner the presence of a reducible hernia.

In cases in which the hydrocele had extended beyond the subcutaneous inguinal ring toward the vulva, the findings were more diagnostic. Palpation was much facilitated, and the mass could be transilluminated. It was also evident that the tumor could not be reduced completely and that it was not an incarcerated hernia.

The oldest patient in the series of 17 was aged 51 years, and the youngest, 28. The average age at the time of operation was 37. In none of the patients had the hydrocele been noted during childhood, and the earliest age at which any patient noticed symptoms was 20 years. The average duration of symptoms was nineteen months. The longest time that a mass had been noticed was sixteen years, and the shortest, two weeks. The duration of the mass, as noticed by the patient, had no relation to its size. Thus, the patient who had the tumor for sixteen years had a hydrocele the size of a plum (about 5 cm. in

62. Counseller, V. S., and Black, B. M.: Hydrocele of the Canal of Nuck: Report of Seventeen Cases, *Ann. Surg.* **113**:625-630 (April) 1941.

diameter) which had not increased perceptibly in size throughout this time. The largest hydrocele had been noted for thirty months and during this time had increased slowly in size.

GENITAL TUBERCULOSIS

Hammond,⁶³ after examining a large number of patients, expresses the view that tuberculosis of the genital tract is a definite entity. Before reaching a diagnosis, cystoscopy must always be carried out. If the urine contains tubercle bacilli and pus, each kidney must be catheterized separately. Tuberculous disease may arise anywhere in the genital tract. The course is chronic, and the symptoms are few. In more than 50 per cent of Hammond's cases, there was roentgen evidence of tuberculous lesions in the lungs. The disease may begin either in the globus major or the globus minor; usually it starts in the latter. At times, especially in cases in which the disease begins acutely, it may involve the entire epididymis at the start and extend along the vas deferens, the lesions being most extensive in the proximal and distal thirds. Sometimes it is associated with marked fibrosis; this has a tendency to contract and thus lead to nodulation or beading of the vas deferens and ultimately to its obliteration—the reason why azoospermia is so frequent. The lesions in the seminal vesicle and the prostate are found at first on the same side as the disease in the testis, and generally those in the vesicle arise before those in the prostate. Later, the opposite vesicle and lobe of the prostate become involved. When this has happened, it is likely that the other testis will be affected. In cases in which the condition is advanced, both testes are involved in 40 per cent. When the prostate is diseased, miliary tubercles and ulcers may be present in the prostatic urethra. Fibrosis may cause narrowing of the urethra; sooner or later it gives rise to back pressure on the kidneys and symptoms of uremia may arise.

Genital tuberculosis runs rather a chronic course with little tendency to dissemination other than in the genital tract. It is characterized by fibrosis rather than by suppuration. It is probable that the bacilli reach the testis by way of the blood stream, that they are taken up by the cells and pass through the seminiferous tubules into the ejaculatory duct; the first lesion is likely to be found where this duct joins the vas deferens. It is possible, however, for the disease to begin in two places in the genital tract at the same time.

The disease occurs in most cases when the patient is between the ages of 20 and 40 years; it rarely occurs in persons under 20. The oldest patient was a man aged 60 years. Generally, the patient presents

63. Hammond, T. E.: Genital Tuberculosis in the Male, *Brit. J. Urol.* **13**: 43-73 (June) 1941.

himself because he has noticed a swelling of the testis. To reach a diagnosis, the physician generally has to be guided by the course which the disease runs. If the swelling is attributable to tuberculosis, it becomes a hard craggy mass that is definitely related to the epididymis. Formation of abscess has been the exception in cases of acute disease. The swelling is generally painless. A characteristic feature is the absence of tenderness and the development of a cold abscess without signs of inflammation. Hydrocele developed in less than 20 per cent of the cases. In only 30 per cent were bacilli found in the urine. Examination of the prostatic urethra with a posterior urethroscope at times revealed miliary tubercles and superficial ulceration.

Treatment in a sanatorium is just as essential for this as for tuberculous disease elsewhere in the body, and epididymectomy or orchidectomy does not in any way remove the necessity of it. It is doubtful whether either of these operations gives better results than those that follow treatment in a sanatorium with division of the vas deferens. The desirability of ligature of the opposite vas as a means of preventing the disease from spreading to the other testis is debatable. New tuberculin is administered every five days, starting with 0.0001 mg. and increasing slowly to 0.001 mg. It should be continued for at least a year after the patient has left the sanatorium. Gold salts are useful if there is much proliferation. The prognosis is that of tuberculosis in general. If the disease does not subside, orchidectomy should be performed. The outlook is dependent on many outside factors.

GONORRHEAL URETHRITIS

Boslow⁶⁴ discusses the treatment of gonorrhea with sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole). This treatment is found to have less toxic effect, and it is demonstrated that sulfathiazole is more rapidly and uniformly absorbed but more rapidly excreted than sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine). Boslow reviews a series of 58 cases of acute gonorrhea. In none of these cases had previous chemotherapy been given. All patients were hospitalized throughout the course of the treatment.

On admission, each patient was given an initial dose of 4 to 5 Gm. of sulfathiazole and then 1 Gm. every four hours for twenty-four hours. The dose was then reduced to 0.66 Gm. every four hours for forty-eight hours. After this period, 0.5 Gm. was given every four hours for ten to twelve days. It was thought advisable to give a large initial dose to avoid the possibility of the formation of sulfathiazole-resistant strains which have been shown to exist in vitro with related compounds. The

64. Boslow, H. M.: Treatment of Gonorrhea with Sulfathiazole, *Mil. Surgeon* 88:659-660 (June) 1941.

drug was given for two weeks, since positive smears and cultures could frequently be shown to exist for several days after the cessation of discharge. Of the 58 patients treated, all but 5 were clinically cured—a cure rate of 91.5 per cent.

There were only three reactions in this series. One consisted of transient headache of twenty-four hours' duration; one was conjunctivitis which lasted for three days, and in 1 case nausea and vomiting occurred on the eleventh day of treatment. The hemoglobin value and the number of leukocytes and erythrocytes disclosed no depressant effect whatever throughout the treatment. No complications developed while patients were undergoing treatment.

Pelouze,⁶⁵ in discussing gonorrhea in male patients, states that sulfanilamide does one of three things for and to patients with gonorrhea: It cures some; it makes symptomless carriers of some, and it fails to have any influence whatever on others. The apparent cure rate obtained with it is so low in comparison with the cure rates achieved with sulfapyridine and sulfathiazole that many careful clinicians are convinced that it is better not to use it for this disease. The cure rate among ambulatory patients is not more than 30 per cent. The toxicity rate is at least 50 per cent. Sulfapyridine, dose for dose, is about as toxic as sulfanilamide; the apparent cure rate is from two and a half to three times greater, and it has the attraction of making few symptomless carriers. Sulfathiazole is unquestionably the best drug of the three for the treatment of gonorrhea by reason of the far lower toxicity rate. The therapeutic value is in every way equal to that of sulfapyridine.

In discussing the highly important question of carriers, Pelouze states that although they still harbor gonococcus and can transmit it to others, they have absolutely no symptoms to suggest its presence. Usually, they can indulge without the slightest return of symptoms in all of those activities that were so potent in the production of symptoms in cases of latent gonorrhea in the old days before sulfanilamide therapy. When they transmit the disease to others, most, if not all, of their victims become totally asymptomatic carriers. They have not the slightest reason to suspect that they have been infected, although careful microscopic or cultural studies will reveal the presence of the gonococcus. When one of these secondarily infected persons transmits the infection to a third person, the latter is left in no doubt, for he has a frank attack of the disease. Socially, these primary and secondary carriers are the greatest present day therapeutic concern. Physicians are not fooled by those who fail to benefit from treatment but can be unmercifully deceived by those who still have the disease but do not present clinical evidences of it.

65. Pelouze, P. S.: *Gonorrhea in the Male: Modern Treatment*, J. Michigan M. Soc. 40:444-448 (June) 1941.

High concentrations of sulfanilamide and its derivatives in the blood are not needed in the treatment of urogenital gonorrhea. Some of the greatest successes have been achieved in cases in which the concentration of the drug used was not more than 1.5 mg. per hundred cubic centimeters of blood. Some failures occurred when the concentration was 15 mg. If sulfanilamide or one of its derivatives is acting favorably, the patient should be entirely free of symptoms by the end of the fifth day. If this does not occur, he can be classed as a definite failure with regard to the drug used, and medication with that particular drug should be discontinued. Then after a few days' rest, the patient should be given another drug; failing of benefit from this, he should be given local treatment.

Conditions which fail to respond to sulfanilamide commonly are favorably influenced by sulfathiazole and sulfapyridine, but the converse is not true. Sulfathiazole commonly acts favorably when sulfapyridine fails. The present custom is to discontinue the administration of sulfanilamide and its derivatives after a week or ten days. There is nothing to suggest that longer medication is needed or of value.

There are many useful schemes of dosage, none of which aim at high concentrations in the blood. The following dosages have been employed by different careful clinicians with about equal curative results:

Days	1	2	3	4	5	6	7	8	9	10
Grams	3	3	3	3	3	3	3			
Grams	4	3	3	2	2	2	2	2	2	2
Grams	3	3	2	2	2	2	2	2	2	2

With these dosages and shortened periods of administration, the toxic factors are at a low ebb; with sulfathiazole they are almost nil.

As a criterion of cure, persistently clear urine for two weeks or longer is of little value. At least 1 out of every 3 patients treated with sulfanilamide and showing this sign is still infected.

By the use of better drugs it is obvious that it is possible to eradicate quickly most gonococcic infection if patients can be kept under treatment for the required length of time. Not only should this be done, but a much longer period of observation should be insisted on after seeming cure than has been generally demanded.

Uhle, Latowsky and Knight⁶⁶ state that sulfapyridine and sulfathiazole are equally efficacious in the treatment of gonorrheal urethritis in male patients. Toxicity is manifested less after treatment with sulfathiazole than after the use of sulfapyridine. Sulfathiazole is the drug of choice for the treatment of gonorrhea. It would seem that a

66. Uhle, C. A. W.; Latowsky, L. W., and Knight, F.: Gonorrheal Urethritis in the Male: Treatment with Sulfapyridine and Sulfathiazole, *J. A. M. A.* **117**:247-249 (July 26) 1941.

combination of oral chemotherapy and local treatment is preferable. Chemotherapy has altered the conceptions of the provocative tests. The value of the culture over the smear in pronouncing a patient cured should be stressed. A social menace is created by the asymptomatic carrier.

A review of the literature⁶⁷ reveals that cases of proved gonococcic pyelonephritis are rare. According to the criteria laid down by Johnson and Hill, only 17 cases have been reported. May reports a case of gonococcic pyelonephritis associated with tuberculosis in the same kidney, bringing the number of cases to 18. Apparently, this is the first report of the occurrence of gonococcic and tuberculous infection in the same kidney.

Proof of the gonococcic nature of the infection was based on the morphologic appearance of the organism found in the renal urine and in pus from the specimen, on the cultural characteristics, including a positive oxidase reaction, on two positive complement fixation reactions, which became negative eleven days after nephrectomy, and on the pathologic findings in the specimen. According to Todd and Sanford, a positive complement fixation reaction is definite evidence of gonococcic infection, and a positive oxidase reaction of colonies which on subculture are found to be growths of gram-negative diplococci is absolute identification of the *gonococcus*.

Since the criteria for diagnosis were established by Johnson and Hill, improved methods of culture and the oxidase reaction have been introduced. These provide additional means of identifying gonococcus.

The symptoms and the clinical findings of gonococcic pyelonephritis are discussed briefly. It is probable that gonococcic pyelonephritis occurs in many cases of gonorrheal infection of the lower portion of the urinary tract and either subsides spontaneously or reacts favorably to treatment for infection of the lower portion of the urinary tract. The fact that in most of the reported cases the condition was unilateral implies that the infection may become chronic only in a kidney made vulnerable to gonococcic attack by some underlying abnormality, usually of an obstructive nature.

Treatment in most of the reported cases of proved gonococcic pyelonephritis, as it was in this case, has been nephrectomy. Sulfanilamide in the dosage of 45 grains (2.91 Gm.) a day for forty-four days, a total of 1,980 grains (128.04 Gm.) was without effect, possibly because of other infection and the extent of the damage to the kidney. Nevertheless, it is believed that rigorous sulfanilamide therapy should be given a trial before more radical treatment is undertaken.

67. May, J. A.: Gonococcal Pyelonephritis: A Complication of Renal Tuberculosis, *J. Urol.* **46**:535-541 (Sept.) 1941.

UROLOGIC OPERATIONS

Priestley, Walters and Counseller,⁶⁸ in discussing urologic operations at the Mayo Clinic during 1939 and 1940, state that the general mortality rate of 1.4 per cent for all urologic operations during 1939 was the lowest ever obtained at the clinic. During 1940, the mortality rate of 2.1 per cent, although higher than that during 1939, was still below the average of preceding years.

Of the various lesions for which operations were performed on the kidney, nephrolithiasis was the most frequent. The hospital mortality rate of approximately 0.5 per cent in 180 cases of renal calculi for 1939 was less than average, while the rate of 4.2 per cent for 1940 was higher than usual. From a surgical viewpoint, discriminative use of nephrostomy not only has reduced the risk of operation but also has improved ultimate results. During the last two years, nephrectomy has been required in 28 to 30 per cent of the operations performed for renal calculi. If more patients with nephrolithiasis were seen earlier during the course of the disease and prior to extensive renal damage, this incidence of nephrectomy could be materially reduced. In general, it has been the experience of Priestley, Walters and Counseller that a renal calculus which is too large to be passed spontaneously and which is lying free in the pelvis or in one of the calices, even though it has caused little renal damage and has resulted in few clinical symptoms, should be removed surgically. If operation is deferred, symptoms usually become more severe and renal damage more extensive—factors which increase the possibility that nephrectomy rather than a conservative operation will be required subsequently. For these reasons, early surgical treatment for nephrolithiasis, as for many other conditions, is preferable. Pelviolithotomy is performed in approximately 50 per cent of all cases of nephrolithiasis, and in approximately 20 per cent of cases nephrolithotomy is required. Nephrostomy, in the surgical management of renal stone, has its greatest usefulness in the presence of long-standing obstruction, excessive infection and extensive renal damage when nephrolithotomy is performed.

Fifty-four patients with staghorn calculi were treated surgically during 1939 and 1940, with 1 death. In 8 of the cases, bilateral stones were present. Conservative operations were performed on 36 kidneys.

In the treatment of hydronephrosis, conservative operations continue to give satisfactory results in many instances. Resection of the renal pelvis and reimplantation of the ureter into the dependent portion of the renal pelvis have proved satisfactory in cases of large hydronephrosis. The use of soft rubber splinting catheters and adequate drainage by

68. Priestley, J. T.; Walters, W., and Counseller, V. S.: Report of Urologic Surgery for 1939 and 1940, Proc. Staff Meet., Mayo Clin. **16**:625-630 (Oct. 1) 1941.

nephrostomy have demonstrated their value on repeated occasions in cases of this type.

Sixty-five patients submitted to operations performed for lesions of the ureter; there was 1 death. Most of these operations were performed for ureterolithiasis. During this same interval, 88 manipulations for ureterolithiasis were performed on 83 patients without death.

During 1939, 70 suprapubic operations on the bladder were performed, with 7 deaths; during 1940, 63 similar operations were performed, with 6 deaths. Many of these operations were performed for neoplastic lesions, and in many cases the patients were in poor condition. Continued development of transurethral procedures greatly reduces the number of indications for suprapubic surgical treatment of vesical lesions. It is felt, however, that total cystectomy could well be used more frequently for carcinoma of the bladder. During 1939 and 1940, total cystectomy was performed for carcinoma of the bladder on 10 patients, with 2 deaths. When total cystectomy is performed in properly selected cases, there is every reason to anticipate that ultimate results will be satisfactory. Although the indications for this operation cannot be dogmatically stated at this time, it is believed that total cystectomy can be employed to advantage in four main types of cases, namely, cases of (1) extensive low grade lesions, (2) low grade lesions of multicentric foci of origin comparable to multiple polyposis of the colon, (3) repeatedly recurring low grade lesions and (4) high grade lesions which, to the best of knowledge, are still confined to the bladder. Some satisfactory immediate results have been obtained during recent years from total cystectomy; it is anticipated that ultimate results may prove to be equally favorable.

During 1939, only 9 suprapubic operations were performed for lesions of the prostate in contrast to 1,000 transurethral resections performed during the same period for benign or malignant prostatic enlargement. During 1940, operations were performed on 60 patients for congenital abnormality of the genital tract, including cryptorchidism, hypospadias and epispadias.

PEYRONIE'S DISEASE

Beach⁶⁹ appeals for universal recognition and sympathetic treatment of Peyronie's disease. He believes that the rarity expressed by statistics is unsubstantiated by diagnostic accuracy, and he details differential diagnoses. Clinical data on 12 patients under observation and treatment for at least nine months are presented. Painful deflected erections are frequently accompanied by conspicuous psychic trends, symptoms corresponding to the degree, the type and the extent of the

69. Beach, E. W.: Peyronie's Disease or Fibrous Cavernositis: Some Observations, California & West. Méd. 55:7-10 (July) 1941.

morbid deviation. Pathognomonic of the disease is an indurated saddle-shaped plaque with well defined edges tightly adherent to Buck's fascia. Fibrous thickening is usually limited to the dorsum; the plaques involve only the septum and/or the tunica albuginea. In most of Beach's cases, localization was in the midline or behind the caput rather than at the base. Hard fibromatous or keloid-like acellular tissue was encountered in the 3 cases in which operation was performed, but inflammatory reaction, implication of the corpus spongiosum, calcific deposits or cartilaginous, osteochondrous or osseous metaplasia were absent. Prognosis should be guarded, as the onset is insidious; its course is unpredictable, and spontaneous regressions are common.

Beach discredits the phylogenetic hypothesis of os priapi but grants certain causative significance to the nobelian bones of the ascaphus, and he illustrates the architectural dissimilarity between the phalli of seals and men and the common anatomic distribution of sclerotic plaques. Incidence of the disease in the fifth and sixth decades suggests a causal relation between retrograde changes of senescence and fibrous cavernositis. Treatment of concomitant pathologic lesions as well as medical fibrolytic therapy is unavailing. Diathermy and irradiation have merits; operation should be highly selective and plastic.

NECROTIC PAPILLITIS

Mellgren and Redell⁷⁰ report 2 cases of necrotic papillitis associated with chronic pyelonephritis. In 1 case signs of urinary stasis (hypertrophy of the prostate) were present. An amyloid-like substance was found in the renal papillae in both cases. This amyloid degeneration was regarded as a predisposing factor in the production of papillary necrosis. The pathologic changes present in cases of necrotic papillitis correspond to a definite clinical picture. In most cases the clinical diagnosis is made by roentgen examination.

EFFECT OF ESTROGEN ON TESTICULAR FUNCTION

Heckel and Steinmetz⁷¹ discuss the effect of estrogen on the function of the human testis. They report several cases in which intramuscular injections of alpha estradiol benzoate were given. In all cases there was marked reduction in the total number of spermatozoa. The other effects on these patients were gradual enlargement and hypertrophy of the breast and a gradual loss of libido; none of the patients, however, became completely impotent.

70. Mellgren, J., and Redell, G.: *Zur Pathologie und Klinik der Papillitis necroticans renalis*, Acta chir. Scandinav. **84**:439-457, 1941.

71. Heckel, N. J., and Steinmetz, C. R.: *The Effect of Female Sex Hormone on the Function of the Human Testis*, J. Urol. **46**:319-321 (Aug.) 1941.

SULFANILAMIDE THERAPY

Thompson, Herrell and Brown⁷² report a case in which anuria occurred after treatment with sulfadiazine (2-[paraaminobenzenesulfonamido]-pyrimidine). On the basis of their experience, it does not appear that sulfadiazine is a drug completely without toxic properties. It is their opinion that the administration of sulfadiazine may be followed by any of the reactions commonly experienced with chemotherapeutic agents which contain the radical of the parent compound, but they believe that sulfadiazine causes less gastrointestinal irritation (nausea and vomiting) than other derivatives of sulfanilamide. Headache, drug fever, dermatitis and leukopenia have been experienced with equal frequency after the administration of this compound.

The authors state that several facts of importance have arisen from the development of anuria in their case. The urinary output of patients receiving chemotherapy should be maintained between 1,200 and 1,500 cc. per day. The formation of crystals will occur as frequently after the administration of this compound as after the administration of either sulfapyridine or sulfathiazole, if the same precautions concerning urinary output are not taken. Acidity of the urine does not appear to be of great significance in the acetylation of this compound. No question of the possible therapeutic effectiveness of sulfadiazine is raised, but grave question is made of the common belief that the compound is relatively safe. The same fundamental principles apply to the administration of this compound as to the administration of the other two compounds which have a similar action, namely, sulfapyridine and sulfathiazole.

Donahue,⁷³ in a discussion of the use of sulfanilamide in genito-urinary wounds, reports 4 cases in which suprapubic prostatectomy was performed for purulent residual urine. With the use of sulfanilamide, the wounds healed by primary intention except for the region occupied by the suprapubic drains. Two of these patients were obese and had thick fatty abdominal walls. In every instance, wounds left by cystotomy likewise healed by primary intention. Sulfanilamide was used also after incision and drainage of a perirenal abscess, the post-operative drainage continuing only a short time. The wound around the drain closed by primary intention.

In conclusion, Donahue states that sulfanilamide powder has proved to be of value in the healing of wounds and may be used without fear of damage to tissue. Further experimental work must be done to determine the minimal effective amounts of sulfanilamide.

72. Thompson, G. J.; Herrell, W. E., and Brown, A. E.: Anuria After Sulfadiazine Therapy, *Proc. Staff Meet., Mayo Clin.* **16**:609-612 (Sept. 24) 1941.

73. Donahue, C. D.: The Use of Powdered Sulfanilamide in Infected Genito-urinary Wounds, *J. Urol.* **46**:562-566 (Sept.) 1941.

Latowsky, Baker, Knight and Uhle⁷⁴ present a study of sulfadiazine in the treatment of gonorrheal urethritis in men. A total of 57 patients were studied, 55 of whom were followed to the completion of the study. Of the 55 patients followed, 93 per cent were cured after an average of eight days of treatment with an average dose of 17.5 Gm. Toxic reactions occurred in only 8.8 per cent of the cases. The average time elapsing before the cultures first became negative for gonococci was thirteen days. The criteria of cure in this study were strict and included as the final provocative test two or more negative smears and cultures of the prostatic fluid.

Neter⁷⁵ states that sulfadiazine has bacteriostatic and bactericidal properties toward *Bacillus coli* isolated from patients with infection of the urinary tract. In a concentration of 100 mg. per hundred cubic centimeters of blood, it was found to be less effective than sulfathiazole, somewhat more effective than sulfanilamide and sulfanilylguanidine and approximately equally as effective as sulfapyridine.

Sulfadiazine had definite bactericidal activity toward *B. coli* in urine. It exerted greater killing power in urine than in mediums that either are favorable for growth (broth) or do not support visible growth of the organisms (phosphate buffer solution).

A patient who had pyelitis due to *B. coli* and enterococcus and who was treated unsuccessfully with adequate doses of sulfanilamide was promptly cured by the administration of sulfadiazine.

Sulfadiazine exerts some bacteriostatic activity toward enterococci isolated from patients with infection of the urinary tract. Toward certain strains it is less effective than equal concentrations (100 mg. per hundred cubic centimeters of blood) of sulfathiazole.

Satterthwaite, Hill and Young⁷⁶ present an analysis of 155 cases of urologic disease in which sulfadiazine was given. The toxicity of sulfadiazine is low. In only 14 of this series of 155 cases was any reaction to the drug observed, and in each case this sensitivity was minimal and quickly disappeared when administration of the drug was stopped. Further, these were all surface reactions and easily observed. Partial reduction in the urinary output, severe leukopenia or anemia did not occur. This is in marked contrast to the action of other derivatives of sulfanilamide.

74. Latowsky, L. W.; Baker, R. B.; Knight, F., and Uhle, C. A. W.: The Treatment of Gonorrheal Urethritis in the Male with Sulfadiazine: An Analysis of Fifty-Seven Cases, *J. Urol.* **46**:89-94 (July) 1941.

75. Neter, E.: The Antibacterial Activity of Sulfathiazole Toward *B. Coli* and Enterococci Isolated from Patients with Infections of the Urinary Tract, *J. Urol.* **46**:95-100 (July) 1941.

76. Satterthwaite, R. W.; Hill, J. H., and Young, H. H.: The Use of Sulfadiazine in Urinary Tract Infections and Gonorrhea and as a Prophylactic to Prevent Postoperative Infections, *J. Urol.* **46**:101-109 (July) 1941.

Forty-four patients with infection of the urinary tract received the drug. Sulfadiazine was found to be efficacious in vivo against *Proteus vulgaris*, *Pseudomonas pyocyanea*, *Escherichia coli*, *Aerobacter aerogenes* and, to a lesser extent, *Staphylococcus albus*. In a series of 14 cases in which operation on the urinary tract had not been performed recently, all but 3 were cleared of their infection.

Fifty cases of gonococcic urethritis were analyzed. Of 30 patients who returned for observation, only 4 failed to respond to sulfadiazine therapy, 86 per cent having negative prostatic cultures and no evidence of any recurrence. These results were obtained with a minimum of toxic reactions. Sulfadiazine offers great promise in the treatment of gonococcic urethritis.

The use of sulfadiazine to prevent or to reduce postoperative complications in cases of urologic disease appears to be successful. In a series of 64 cases in which the patients were treated either before operation or both before and after with sulfadiazine, there has been only a single instance of transitory bacteremia.

Helmholz⁷⁷ states that according to observations in vitro sulfathiazole is definitely superior to sulfanilamide as a urinary antiseptic in concentrations of 10 to 30 mg. per hundred cubic centimeters of urine. The bactericidal action of sulfathiazole in concentrations of 10 mg. per hundred cubic centimeters of urine brings it well within the range possible for therapeutic use for urinary infection in cases in which the kidneys are badly damaged. From Helmholz' experience, the doses used in these cases were too large, and doses of 0.3 to 0.65 Gm. (5 to 10 grains) per day deserve a trial.

METHENAMINE MANDELATE AS A URINARY ANTISEPTIC

Kirwin and Bridges⁷⁸ report their findings in a clinical investigation of the urinary antiseptic methenamine mandelate. They state that although mandelic acid and methenamine have both been used extensively as urinary antiseptics, their toxic effects, particularly after long-continued administration, have seriously limited their employment.

The chemical combination of these two drugs having been found practical, the authors made use of methenamine mandelate in the treatment of a group of patients. In 63 cases in which full data were available, excellent results were obtained. An average dosage of three

77. Helmholz, H. F.: A Comparison of the Bactericidal Effect of Low Concentrations of Sulfanilamide and Sulfathiazole on Bacteria from Urinary Infections, *J. Urol.* **46**:322-331 (Aug.) 1941.

78. Kirwin, T. J., and Bridges, J. P.: Studies in Urinary Antisepsis: Clinical Investigation of Mandelamine, a Recently Introduced Urinary Antiseptic, *Am. J. Surg.* **52**:477-480 (June) 1941.

tablets, each consisting of 0.25 Gm. of methenamine mandelate, given three times daily, readily controlled most of the common urinary infections and maintained a urinary acidity below pH 6.0 without the use of any accessory administration of acid. In the majority of cases the urine cleared within three to five days, and such symptoms as frequency and urgency of urination were reduced or entirely eliminated.

None of the patients manifested toxic symptoms at any time. This demonstrated that the effectiveness of methenamine as a urinary antiseptic has not been impaired by its chemical combination with mandelic acid, although nausea, vomiting and other gastrointestinal disturbances induced by large doses of mandelic acid have been eliminated.

ENURESIS

Spence,⁷⁹ in discussing enuresis, states that there should be a general sizing-up of the patient by a pediatrician and a brief period of conservative medical treatment. If this regimen is unsuccessful or if at any time pyuria, hematuria, fever or any other symptoms suggestive of genitourinary disease are present, there should be a thorough investigation by a urologist. Major disease will thus be detected and appropriate treatment carried out.

In the majority of cases of refractory enuresis in girls, chronic granular urethritis will be found to be the basis and its response to treatment is most gratifying. The necessary dilations can be carried out easily by either the urologist or the pediatrician. In boys with refractory enuresis, after major disease and pinpoint meatus are excluded, dilation and instillation are satisfactory.

PREVENTION OF POSTOPERATIVE URINARY RETENTION

Helfert and Granet⁸⁰ discuss the prevention of acute urinary retention following anorectal and perineal surgical procedures. In 140 cases in which anorectal or perineal urologic operative procedures were performed, 30 cc. of a 0.5 per cent aqueous solution of mercurochrome was instilled into the urinary bladder on completion of the operation. Acute urinary retention requiring catheterization occurred in only 1 case (0.8 per cent). In a previous series of 100 similar cases in which mercurochrome was not used, acute urinary retention requiring catheterization occurred in 57.

79. Spence, H. M.: Urologic Aspects of Enuresis, *South M. J.* **34**:830-833 (Aug.) 1941.

80. Helfert, I., and Granet, E.: Prevention of Acute Urinary Retention Following Anorectal and Perineal Surgical Procedures, *Am. J. Surg.* **53**:129-130 (July) 1941.

URINARY SYMPTOMS IN GYNECOLOGIC DISEASE

Hochman,⁸¹ in a review of 500 gynecologic patients with urinary symptoms, states that urinary symptoms in the great majority of cases have their origin in the vesicourethral junction. In such cases, meticulous examination of the urethra, the neck of the bladder and the bladder should be carried out.

Correction of gynecologic disease and abnormal physiologic changes is frequently followed by alleviation of urologic symptoms. Consideration of the patient's history, particularly in regard to menopause, marital status, mental health, age and other factors, is important in deciding on treatment. Dilation of the urethra is of definite value in the treatment of diseases of the vesicourethral junction. Hydrotherapy, general hygienic measures and proper sedation should accompany local treatment. The term "cystitis," so frequently used as a diagnosis to cover urinary symptoms, should be replaced by a term applicable to the specific pathologic process found. The gynecologist should have proper training in cystoscopy and endoscopy of the urethra.

URACHAL STONE

Dreyfuss and Fliess⁸² report a case of patent urachus with the formation of stone. The patient, a girl aged 11 years, died shortly after entering the hospital. At the age of 5 years she had had pyuria and had passed stone. Later, she had shown evidence of cystitis and pyelonephritis. Shortly before entering the hospital, she became desperately ill and had convulsions. The urine contained pus and albumin, and the number of leukocytes was increased. At necropsy, the urinary bladder was found to be large and thickened. It extended up the umbilicus, and its fundus was adherent to it. The ureteral openings were hidden by folds of edematous mucosa but were patent. A light brown stone, 4 cm. long and 1.8 cm. wide, was firmly lodged in the upper segment. The stone consisted of uric acid. The final anatomic diagnosis was persistent fetal bladder with severe inflammation and formation of stone.

CHANGES IN THE PHYSICAL PROPERTIES OF SEMEN

Hotchkiss⁸³ states that there were wide variations in the volume, the number of cells and the motility of the spermatozoa in 642 specimens

81. Hochman, S.: A Review of Five Hundred Gynecological Patients with Urinary Symptoms, *Am. J. Surg.* **52**:472-476 (June) 1941.

82. Dreyfuss, M. L., and Fliess, M. M.: Patent Urachus with Stone Formation, *J. Urol.* **46**:77-81 (July) 1941.

83. Hotchkiss, R. S.: Factors in Stability and Variability of Semen Specimens: Observations on Six Hundred and Forty Successive Samples from Twenty-Three Men, *J. Urol.* **45**:875-888 (June) 1941.

of semen submitted by 22 men. The morphologic types exhibited relatively less fluctuation than did the other three characteristics of the semen. The viscosity of seminal specimens varies considerably.

Frequent coitus tends to reduce the volume and the number of cells without materially altering the motility and the appearance of spermatozoa. Sexual abstinence for seventy-two hours promotes uniformity of specimens but does not eliminate wide variations that can be explained by losses in collection of the specimen, laboratory errors or minor alteration in health and habits. Men tend to hold to certain levels from which deviations take place. The clinical importance of such fluctuations is particularly significant in marginal specimens. Illness may have an adverse effect on semen, which is most marked about thirty days after the disturbance in health. Recovery takes place at a slightly slower rate.

OPERATION ON THE VENA CAVA

Hyman and Leiter⁸⁴ report a series of 11 surgical procedures on the vena cava. Experimental and surgical procedures have demonstrated that complete ligation of the vena cava below the renal veins is compatible with life. In 4 cases of this series, the vena cava was accidentally injured, while in the other 7 cases surgical operation was deliberate. The deliberate type of operation on the vena cava is generally associated with renal neoplasms or adherent pyonephrotic kidneys. With the newer sulfanilamide preparations in general use, the indications for operation on the vena cava in inflammatory conditions will be reduced to a minimum. Death occurred postoperatively in 3 of the 11 cases. The authors stress that the renal vein and the vena cava should always be explored in cases of right renal neoplasm. For this reason, a wide exposure, necessitating resection of one or two ribs, is advisable. In some of the cases reported, the patient survived a three year period during which thrombi were present in the vena cava. The presence of a tumor thrombus in the vena cava, while certainly grave, does not necessarily imply an immediately fatal course.

APPENDICAL CALCULUS

Guido⁸⁵ reports a case of appendical calculus which simulated ureteral calculus both in the roentgenograms and in the symptoms.

He states that true calculus of the appendix is always visible roentgenographically but that because of its rarity, the shadow is usually mistaken for ureteral calculus. Commonly, the ureter also is obstructed

84. Hyman, A., and Leiter, H. E.: Surgery of the Inferior Vena Cava in Urologic Conditions, *J. Urol.* 45:813-826 (June) 1941.

85. Guido, F. R.: Appendiceal Calculus: Report of Case, *California & West. Med.* 55:19-22 (July) 1941.

at the point of the shadow, the obstruction being caused by an inflamed appendix adherent to the ureter or by the proximity of the appendical calculus to the ureter.

In Guido's case, the patient was a man aged 38 years. He had not had urinary symptoms; the urine was normal, and there was no pain or tenderness over the right lower quadrant of the abdomen. A roentgenogram revealed a huge calculus in the upper part of the true pelvis at the lower margin of the sacroiliac joint. Intravenous pyelograms did not reveal evidence of dye in the right side. Consequently, a diagnosis of calculus of the lower third of the right ureter was made. The ureter was exposed, but calculus was not seen. The peritoneal cavity was then opened, and calculus was found in the appendix.

In this case, the calculus in the appendix was not typical of ureteral stone. It was large, shaped like a ureteral stone and slightly out of line with the ureter.

RETENTION CATHETER

Owens⁸⁶ reports a seemingly essential modification of the bag catheter. In some of the catheters in use at present the bag dilates only on one side of the catheter, commonly causing the catheter to angulate and at times become obstructed. In Owens' modification, the bag enlarges uniformly around the catheter.

86. Owens, C. A.: A Modified Bag Catheter, *J. Urol.* **46**:344-345 (Aug.) 1941.

CORRECTION

In the article by Dr. Robert Gutierrez, "Large Solitary Cysts of the Kidney: Types, Differential Diagnosis and Surgical Treatment," in the February issue (*ARCH. SURG.* **44**:279, 1942), the word "laparotomy" in the third line from the bottom of page 314 should read "lumbotomy."

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TUMORS OF THE PALATE (BENIGN AND MALIGNANT)

HAYES MARTIN, M.D.

Attending Surgeon, Memorial Hospital for the Treatment
of Cancer and Allied Diseases

NEW YORK

The palate, hard and soft, gives rise to a varied group of tumors—epidermoid carcinoma, adenocarcinoma and benign mixed tumors. Melanoma, lymphosarcoma and myosarcoma occur only rarely in this structure. In most parts of the oral cavity malignant tumors can be reasonably separated from benign tumors. Such definite separation is impossible in the palate, where there is a gradual transition in the cellularity of benign tumors into cancer. The title of this report is therefore "Tumors [rather than Cancer] of the Palate."

The present report is based on a series of all patients with neoplasms of the hard and soft palates admitted to the Memorial Hospital for the Treatment of Cancer and Allied Diseases from 1929 to 1936, inclusive. Of those with malignant tumors, none have been excluded because of the advanced stage of the disease.

DEFINITION

The term "tumors of the palate" should be limited to growths arising on the inferior, or oral, surface of the hard and soft palates (roof of the mouth). The upper surface of the hard and soft palates forms the floor of the nasal cavity and of the nasopharynx, respectively, and growths which arise on this surface are classified as nasal cavity or nasopharyngeal, rather than palatal, tumors.

In the English language there is no term to differentiate the bone of the hard palate from the overlying soft tissue, although in German *Gaumen* designates the soft tissues covering both the palate and the alveolar processes. Since growths of the bony hard palate are extremely rare, the lack of such a term in English causes no confusion. In the present discussion the terms "hard palate" and "soft palate" will be used to refer only to the soft tissues, in which practically all palatal tumors arise.

From the Head and Neck Service, Memorial Hospital for the Treatment of Cancer and Allied Diseases.

The palate is the site of origin of a greater percentage of benign "mixed" tumors of salivary gland type than is any other structure in the head and neck except the parotid salivary gland, as will be discussed in more detail. These tumors are almost identical in histologic nature and in clinical course with mixed tumors of the parotid gland. Wherever they arise, it is sometimes difficult, both histologically and clinically, to distinguish between cellular benign mixed tumor and cancer. It is obvious that some benign mixed tumors after varying periods of quiescence may change in character, certain elements becoming frankly malignant (carcinomatous), and pursue a malignant course.

The term "cancer of the palate" includes two main histologic groups: (1) epidermoid carcinoma arising in the squamous epithelium and (2) the adenoid tumors arising in minor salivary and mucous glands, consisting mainly of adenocarcinomas. For purposes of statistical analysis it is essential that these histologic groups be considered individually as well as collectively, since they differ markedly in etiology, incidence, clinical course and response to treatment.

ANATOMY OF THE PALATE

The palate, which forms the roof of the mouth, is divided anatomically into the hard palate anteriorly and the soft palate posteriorly. The bony hard palate consists of the palatal processes of the maxilla anteriorly fused with the horizontal parts of the palate bones posteriorly, this bony structure being covered on its inferior surface by periosteum, a layer of fibrous tissue and submucosa, and finally mucous membrane. In the anterior portion of the hard palate these soft tissues present a number of transverse ridges, the plicae palatinae, which are strongly developed in carnivora.

The soft palate is attached anteriorly to the posterior margin of the hard palate and is continuous laterally with the supratonsillar fossae and the tonsillar pillars. The latter curve upward and backward to form the posterior free edge of the soft palate, in the center of which is the uvula. The soft palate (5 to 7 mm. in thickness) consists of a strong fibrous sheet covering the palatine aponeurosis, in which are attached several muscles (musculi pharyngopalatini, uvulae, levatores veli palatini, tensores veli palatini and glossopalatini) covered on both upper and lower surfaces by stratified squamous epithelium over a submucosa of relatively loose areolar tissue. By virtue of its intrinsic musculature, the soft palate performs an important function during the act of swallowing—that is, closure of the opening into the nasopharynx—and invasion of this musculature by cancer or erosion of the palate by a growth is attended by marked disability both in swallowing and in speaking.

The submucosa of both the hard and the soft palate contains a great number of racemose and mucous glands; these glandular structures

increase in number toward the posterior margin of the soft palate, so that they make up most of the body of the uvula. The abundance of these glandular structures accounts for the frequency of adenoid tumors in the palate.

The blood supply of the palate consists of a number of small arterial branches (descending palatine, nasal septal, ascending palatine and others) which arise from the internal maxillary, external maxillary, ascending pharyngeal and lingual arteries. None of the branches in the palate itself is large enough to permit excessive hemorrhage. Serious bleeding in palatal cancer occurs almost always from erosion of larger arteries in adjacent structures.

ANATOMY OF THE LYMPHATICS OF THE PALATE

The finer lymphatics of the hard and soft palates are continuous with each other and with those of the gums and of the palatine tonsils. The finer capillary network gives origin to collecting trunks which pass backward to reach the retromolar triangle and from this point follow three different routes to reach the internal jugular chain, the submaxillary nodes and the retropharyngeal nodes, respectively. From these several groups of nodes the efferent lymph drainage passes into the middle and lower nodes of the internal jugular chain.

According to anatomists,¹ the main lymphatic pathway from the retromolar triangle is downward along the anterior border of the ascending ramus, mesial to the horizontal ramus and the submaxillary salivary gland, and then to the inner side of the posterior belly of the digastric muscle to the subdigastric lymph nodes of the internal jugular chain. The behavior of metastases in the present series proves the predominance of the latter pathway, since in over 75 per cent of the cases with metastasis the subdigastric nodes were the first to be involved.

The anterior lymphatic trunks of the palate first pass backward over the upper gums posterior to the third molar tooth and immediately penetrate deeply into the tissues of the cheek, where they join the lymphatics of the buccal mucosa, pierce the buccinator muscle and descend along the course of the external maxillary blood vessels to the prevascular and retrovascular lymph nodes of the submaxillary group. The anterior pathway to the submaxillary nodes is said by anatomists to be inconstant, a view not fully supported by the observations at the Memorial Hospital, since in a considerable number of the cases in the present series (16 per cent of those with metastases) the first node involved was in the submaxillary group.

1. Rouvière, H.: *Anatomy of the Human Lymphatic System*, translated by M. J. Tobias, Ann Arbor, Mich., Edwards Brothers, Inc., 1938. Sassier, P.: *Lymphatiques de la voute palatine, du voie du palais et de la luvette*, Ann. d'anat. path. 4:933, 1927.

Anatomists refer to a third and rare pathway by which a few collecting trunks pierce the pharyngopalatinus muscle and the superior constrictor of the pharynx to enter the retropharyngeal space and empty into the lateral retropharyngeal node; but at the Memorial Hospital my associates and I have never been able to demonstrate metastasis to the retropharyngeal nodes from cancer of the palate.

ETIOLOGY

General Incidence.—According to the admission records of the Memorial Hospital, malignant tumors of the palate (excluding benign mixed tumors) make up about 8 per cent of all oral cancer, about 5 per cent of all cancer of the upper respiratory and alimentary tracts and about 2 per cent of all human cancer. The incidence ratio of malignant growths to benign mixed tumors in the palate is 12 to 1.

Most reports in the literature agree that the palate is the most frequent site of origin of adenoid tumors (adenocarcinomas and mixed tumors) in the oral cavity. Watson² in 1935 reported a series of 46 adenocarcinomas of the oral cavity from the Memorial Hospital and found that over 50 per cent arose in the palate. Abshier³ stated that with the exception of the parotid and salivary glands the palate is the most frequent site of mixed tumors. In the New and Childrey⁴ series of 74 cases of "adenocarcinoma of mixed tumor type" in the tonsil and the pharynx (including the palate) 56 per cent of the tumors were in the palate. In the present series of 103 palatal tumors, 24 (24 per cent) were of the adenoid type, a figure less than that reported by Ahlbom,⁵ who stated that of 62 palatal tumors treated at Radiumhemmet between 1921 and 1932, 35 per cent were of the mucous and salivary gland type.

Many authors erroneously consider mixed salivary gland tumors of the palate to be extremely rare. Sonnenschein⁶ in 1929 was able to collect less than 50 cases from a complete survey of the literature, and

2. Watson, W. L.: Adenocarcinoma of the Oral Cavity, *Am. J. Roentgenol.* **34**:53, 1935. Watson, W. L., and Pool, J. L.: Cancer of the Thyroid, *Surg., Gynec. & Obst.* **70**:1037, 1940.

3. Abshier, A. B.: Mixed Tumors of the Palate, *Arch. Dermat. & Syph.* **32**:622 (Oct.) 1935.

4. New, G. B., and Childrey, J. H.: Tumors of the Tonsil and Pharynx: II. Adenocarcinomas of the Mixed Tumor Type, *Arch. Otolaryng.* **14**:699 (Dec.) 1931.

5. Ahlbom, H. E.: Mucous- and Salivary-Gland Tumors, *Acta radiol.*, 1935, supp. 23, p. 1.

6. Sonnenschein, R.: "Mixed" Tumors Occurring in the Soft Palate with Reports of Two Cases and a Survey of the Recent Literature, *Tr. Am. Laryng. A.* **51**:235, 1929.

in 1937 Rhoads and Mecray⁷ stated that only 12 new cases had been recorded since Sonnenschein's report. The paucity of reports in the literature gives a false idea of the incidence of this tumor, which is undoubtedly more frequent than the figures indicate. The long duration with few symptoms for the benign and even for some of the malignant tumors is undramatic, and in the older age group the patients are likely to die of other causes rather than of their primary tumors. When systemic metastasis occurs long after the control of the primary lesion in a case of adenocarcinoma, it is probable that the association with the former palatal tumor is often not realized.

Age Incidence.—The average age on admission in the present series of 103 cases of palatal tumors (benign and malignant) was 57 years, which is about the same as that in cases of intraoral cancer in general. There was a noteworthy difference in the mean ages of patients with epidermoid carcinoma (61 years), with adenocarcinoma (48 years) and with benign mixed tumors (37 years). This difference becomes even more apparent when the average ages at the beginning of symptoms are calculated. The duration before admission in cases of epidermoid carcinoma (seven months) was relatively short compared with the duration (about three years) in cases of the adenoid group (adenocarcinoma and mixed tumors). According to the histories of the 2 oldest patients with mixed tumors the duration of the lesions was twenty-five and nine years, respectively. The mean ages of the patients at the onset of symptoms were: epidermoid carcinoma, 60 years; adenocarcinoma, 46 years; mixed tumors, 31 years. In brief, epidermoid carcinoma of the palate is a disease of old age, while adenoid tumors occur mainly in the young or middle aged and almost always before the age of 45. In the series of cases of intraoral adenocarcinoma from the Memorial Hospital analyzed by Watson, the average age was 49 years; and New and Childrey⁴ in 74 cases of adenocarcinoma of the pharynx (including the palate) and the tonsil found the average age to be 45.5 years. In Ahlbom's⁵ report the age incidence is calculated on the combined groups with parotid, submaxillary and mucous membrane tumors, but the general trend agrees with the aforementioned figures, that is, the average age of patients with benign and semimalignant mucous and salivary gland tumors is given as 43 years, while for patients with malignant tumors the corresponding age was 52 years. Ahlbom also called attention to the significance of calculations based on the time of the beginning of symptoms in these groups of cases.

In the records of the Memorial Hospital there are 2 cases of myosarcoma of the palate, both the patients being female children, 7 and 9 years, respectively. One of these cases is included in the present series.

7. Rhoads, J. E., and Mecray, P. M., Jr.: Recurrence in Mixed Tumors of the Soft Palate, *Am. J. M. Sc.* 193:389, 1937.

Sex Incidence.—There was a noteworthy difference in sex distribution between the epidermoid and the adenoid tumors of the palate. For epidermoid carcinoma in this area the sex distribution (90 per cent in males; 10 per cent in females) was about the same as for epidermoid carcinoma of the oral cavity in general. The adenoid tumors of the palate affected females (58 per cent) more often than males (42 per cent). Watson found that adenocarcinoma of the oral cavity in general was distributed about equally between the two sexes.

There is not complete agreement in the literature on the sex incidence of mucous and salivary gland tumors. Some authors⁸ have reported different degrees of predominance in men. Others⁹ have reported about an equal incidence in the two sexes. Even an equal distribution between the sexes would be of significance, since other tumors in this area (epidermoid group) are found predominantly in males (80 to 95 per cent). In this connection it might be of interest to mention that according to the records of the Memorial Hospital certain other forms of glandular cancer are found preponderantly in females, namely, cancer of the parotid gland (60 per cent), adenocarcinoma of the skin (60 per cent) and cancer of the thyroid gland (70 per cent). The most definite exceptions to this rule are cancer of the stomach (75 per cent in males) and cancer of the rectum (66 per cent in males).

The female preponderance (58 per cent) of adenoid tumors of the palate in the present series may be coincidental only, since the difference is not great and the series is small. This figure is identical, however, with that obtained by Ahlbom⁵ in 254 cases of mucous and salivary gland tumors, including parotid and submaxillary salivary gland tumors. Ahlbom found an even greater female preponderance (65 per cent) in 130 patients with benign and semimalignant tumors alone. Kennon¹⁰

8. Heineke, H.: *Bösartige Geschwülste der Speicheldrüsen*, in Zweifel, P. P., and Payr, E.: *Die Klinik der bösartigen Geschwülste*, Leipzig, S. Herzel, 1924, vol. 1, p. 760. Nyström, G.: *Kräftsjukdomarne i Sverige*, Stockholm, Svenska Tryckeriaktiebolaget, 1922; cited by Ahlbom.⁵ Pack, G. T., and LeFevre, R. G.: *The Age and Sex Distribution and Incidence of Neoplastic Diseases at the Memorial Hospital, New York City*, *J. Cancer Research* **14**:167, 1930. Rodriguez, L.: *Contribution à l'étude du sarcome pur de la parotide*, Thesis, Paris, no. 240, 1890. New and Childrey.⁴

9. Benedict, E. B., and Meigs, J. V.: *Tumors of the Parotid Gland: Study of Two Hundred and Twenty-Five Cases with Complete End Results in Eighty Cases*, *Surg., Gynec. & Obst.* **51**:626, 1930. Schreiner, B. F., and Mattick, W. L.: *Tumors of the Salivary Glands Based on a Study of Sixty-Six Cases*, *Am. J. Roentgenol.* **21**:541, 1929. Stein, I., and Geschickter, C. F.: *Tumors of the Parotid Gland*, *Arch. Surg.* **28**:491 (March) 1934. Stöhr, F., and Risak, E.: *Zur Klinik und Anatomie der Parotisgeschwülste*, *Arch. f. klin. Chir.* **143**:609, 1926. Sonnenschein.⁶

10. Kennon, R.: *Tumours of the Salivary Glands with Their After-History*, *Brit. J. Surg.* **9**:76, 1921.

and Hintze¹¹ also reported a female preponderance (66 per cent) for parotid mixed tumors. Although the voluminous statistical material is sometimes contradictory, it is significant that among those authors who have subjected their material to the most careful analysis the trend toward reporting a higher incidence in females is rather definite.

Position of the Growth.—Neoplasms occur more often in the soft than in the hard palate. The majority of epidermoid carcinomas occur on the soft palate, and the posterior edge of this structure is more often involved than any other part. Epidermoid carcinomas tend to occur on the soft palate (73 per cent) more often than on the hard (27 per cent), while with mucous and salivary gland tumors the ratio is reversed (43 per cent in the soft palate and 57 per cent in the hard). Ahlbom⁵ found the occurrence of salivary gland tumors to be higher in the hard palate (16 cases) than in the soft (6 cases). Epidermoid carcinomas are fairly well distributed between the two sides and the center of the palate, whereas adenocarcinomas practically always arise on one side or the other of the midline. In the present series none appeared directly in the midline. The right and left sides were involved in about equal percentages of cases.

Causative Factors.—After a consideration of the etiology, the morbid anatomy and the clinical course it becomes obvious that different factors must operate to produce, respectively, epidermoid and adenoid tumors of the palate. Epidermoid carcinoma arises in patients of the older age group, in whom the mucous membranes have suffered the characteristic degenerative changes of the aging process. In patients with tumor of this type there is the usual high percentage of precancerous changes in the oral mucous membranes (leukoplakia, chronic glossitis, atrophy) which result from extraneous irritants. As with all forms of epidermoid cancer of the mucous membranes or skin, the sex distribution is predominantly male (85 to 95 per cent). On the other hand, adenoid tumors (malignant and benign) occur about fifteen years earlier; mucous membrane changes due to extraneous irritants are uncommon, and the sex distribution is preponderantly female.

In the epidermoid group of the present series there was evidence of subacute or chronic irritation of the mucous membrane (leukoplakia, glossitis, atrophy) in about 35 per cent of the cases, which approaches the incidence of such abnormalities in the general group of intraoral cancer. In the adenoid group there was no evidence of subacute or chronic irritation in any of the cases. It is more difficult with palatal cancer than with the average intraoral growth to demonstrate (either by history or by objective findings) the influence of the more common

11. Hintze, A.: Gutartige und bösartige Parotisgeschwülste und ihre Heilungsmöglichkeiten, Arch. f. klin. Chir. 180:606, 1934.

forms of chronic irritation, namely, syphilis, tobacco and trauma from dentures. The same is true of the stomatitis following dietary deficiencies, mainly avitaminosis B, of which little evidence was noted in the present series.

Leukoplakia.—Any form of long-standing chronic irritation of mucous membranes may result in leukoplakia or cancer or both in the same patient. Leukoplakia was specifically noted in 27 per cent of the patients with epidermoid carcinoma in the present series. It was absent in all of the group with adenoid tumors.

Syphilis.—In the present series Wassermann tests were made in 58 cases, and all gave negative reactions. Although this negative finding is probably accidental, it is nevertheless a strong indication that syphilis plays no significant role in the etiology of palatal cancer. In contrast, about 30 per cent of the patients with cancer of the tongue in the Memorial Hospital have positive Wassermann reactions. The degenerative changes in the oral mucous membrane in chronic syphilis (leukoplakia and atrophy) are most frequent and marked on the tongue but in most cases spread also to the gums, the cheeks and the palate.

Tobacco.—In heavy pipe smokers there is a tendency toward epithelization of the palatal mucosa where the stream of hot smoke strikes the roof of the mouth. This change differs somewhat in appearance from the average leukoplakia of the oral cavity, that is, the palatal mucosa is greatly thickened and often presents a variable number of small to large round elevated papillary projections, somewhat resembling the circumvallate papillae in appearance. If one of these is removed when small, it is difficult to prove histologically anything further than chronic inflammatory changes, but larger lesions usually show papillomatous overgrowth of the epithelium. Although common in pipe smokers, such changes in the palatal mucosa are rarely seen in association with cancer, and there is little statistical evidence to indicate that they have any great importance from the standpoint of cancerigenesis. In the present series about 60 per cent of the patients reported past or present use of tobacco—an incidence slightly below that of the tobacco habit in cases of intraoral cancer in general (70 to 75 per cent). Mucous membrane changes seldom result in the soft palate from the tobacco habit, except in heavy cigar smokers (those who smoke fifteen to twenty a day), in whom the soft palate and the base of the tongue become deep red and congested with marked hypertrophy of lymphoid tissue. Cancer of the base of the tongue or soft palate associated with heavy cigar smoking (an expensive habit) has been termed "rich man's cancer."

Dental Trauma.—Dental diseases and defects, including sharp or worn teeth, should have little significance in the etiology of palatal cancer,

since the teeth do not come into contact with the palate. Of the entire group, about one third of the patients were edentulous in the upper jaw, and only 4 believed that the upper dental plate had irritated the palate. It would be logical to suppose that when an upper dental plate completely covering the gums and the hard palate is kept in place constantly and not removed for cleansing, there would be a retention of partly decomposed secretions and debris between the plate and the palate and that such an accumulation would frequently produce sufficient chronic irritation to cause cancer. It is significant that such an association is rarely found. None occurred in the present series. Recently, however, I have observed epidermoid carcinoma at the junction of the hard and soft palates in a patient who had worn the same full upper dental plate for fifteen years. Retention of this plate had been obtained by undercutting, and the device was so difficult to remove that it was left in place; the patient had gone to his dentist at intervals of not less than six months,

TABLE 1.—*Duration of Symptoms and Size of Lesion in 101 Cases of Tumor of the Palate*

Histologic Type	Duration of Symptoms Before Admission	Av. Size of Lesion on Admission (Cm.)
Epidermoid carcinoma	7 mo.	3.5
Adenocarcinoma	27 mo.	3.0
Benign mixed tumors	5 yr.	4.5

and often more than a year, for cleaning and reinsertion. In this instance the growth had occurred not directly under the plate but at its posterior margin.

SYMPTOMS, MORBID ANATOMY AND CLINICAL COURSE

The three main histologic varieties of palatal cancer—epidermoid carcinoma, adenocarcinoma and mixed tumor—differ in symptoms, morbid anatomy and clinical course, and will therefore be considered separately from these standpoints. The variations in duration of symptoms and size of lesion on admission are given in table 1. The relatively short average duration (seven months) of epidermoid carcinoma and the large average size on admission (3.5 cm.) indicate that this tumor grows rapidly as compared with the adenoid group. The average duration of symptoms of adenocarcinoma is about four times as long (twenty-seven months) as that of epidermoid carcinoma, and the average size of the former tumor (3 cm.) is somewhat smaller. New and Childrey reported an average size of adenocarcinomas of the oral cavity of 5 cm. One of the most outstanding characteristics of mixed tumors is the long duration (average, over five years in the present series; twenty-five years

in 1 case); another is the slow, symptomless growth which permits these tumors to reach an unusually large average size (4.5 cm.).

The hard palate is in almost constant contact with the tactly sensitive tip and dorsum of the tongue, so that irregularities of the palate cannot long escape the attention of an alert patient. The base of the tongue, which lies in contact with the soft palate, does not possess tactile sensation, but ulcerated lesions of the soft palate are more likely to be painful in the early stages, since this structure is functionally mobile during swallowing.

Epidermoid Carcinoma of the Palate.—In the present series the most common site of origin of epidermoid carcinoma was in or near the free edge of the soft palate (73 per cent) with about 22 per cent of the tumors

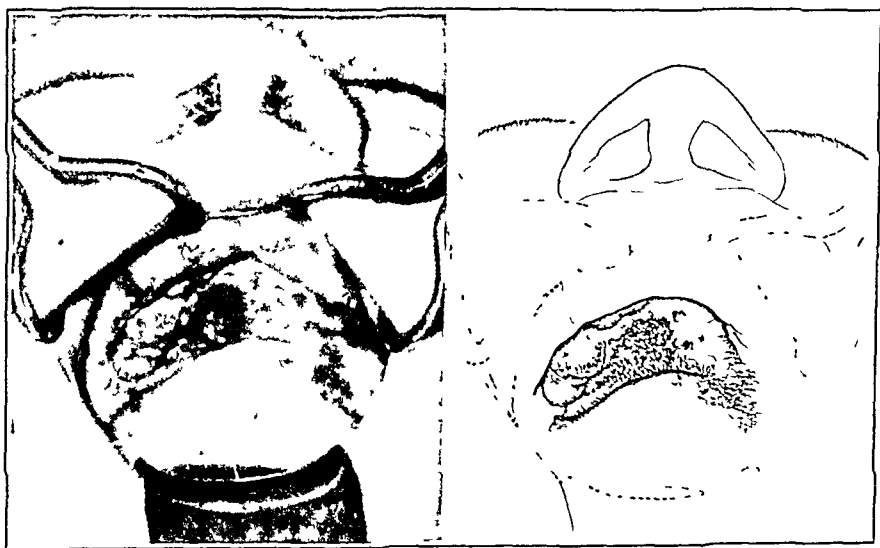


Fig. 1.—Epidermoid carcinoma of the palate. Epidermoid carcinoma of the palate is likely to be a flat, thin, ulcerated, granular lesion; adenocarcinoma in this area is usually raised, ovoid, moundlike and only partly ulcerated; benign mixed tumors are rarely ulcerated.

originating in the hard palate and about 5 per cent at the junction between the two. From the appearance of the earlier lesions it seems that the growth begins as a small superficial granular ulcer with raised rolled edges which tends to fungate from rather than to infiltrate the mucous membrane (fig. 1).

There are apparently few subjective symptoms in the early stages, since in the present series the average diameter of the primary lesions on admission was about 3.5 cm. The most common first symptom (in over 40 per cent of the cases) was the discovery of the lesion itself as a painless irregularity of the mucous membrane. When the growth arises

in the hard palate, there is no interference in function until it is far advanced and infected; then an upper dental plate may become ill fitting or mastication may be painful. As the growth extends, the periosteum overlying the hard palate resists invasion for a time, so that erosion of bone is always a late complication. In the present series it had occurred before admission in only 2 cases, in 1 of which there was perforation into the nasal cavity. Less than 10 per cent of the patients complained of pain or discomfort as the first symptom; it was more common in the soft palate than in the hard.

When the growth arises in the soft palate, pain on swallowing occurs when there is sufficient erosion to permit of deep infection and inflammation of this movable structure. With invasion of the intrinsic musculature there is limitation of the normal elasticity and range of motion of the soft palate, which when functioning normally rises to close off the opening into the nasopharynx during the act of swallowing. As a result of this interference with function, liquid ingesta tend to enter the nasal cavity and to be expelled through the nose. This complication becomes more severe with actual erosion through the soft palate. Normal speech is also altered by any disability of the soft palate.

If uncontrolled locally, epidermoid carcinoma of the palate finally invades and erodes the palate widely, extending onto the pharyngeal walls and the mucosa of the cheeks, producing trismus of the jaws, intractable pain and sepsis. In the unsuccessfully treated patients in the present series, death resulted with about equal frequency from local recurrences at the primary site and from metastasis to the neck or systemic metastasis.

Adenoid Tumors of the Palate.—Adenocarcinoma and mixed tumors of the palate have the same histogenesis, and there is little to distinguish them from the standpoint of clinical appearance and morbid anatomy. They both exhibit the same slowly growing, sharply delimited ovoid submucous mass. They differ mainly in that adenocarcinoma has a slightly more rapid rate of growth and may eventually metastasize, while mixed tumors grow more slowly and do not disseminate beyond the point of origin. Except in their more advanced stages, these two forms of palatal tumors can be differentiated only by histologic examination. On the other hand, the adenoid tumors can be differentiated readily from epidermoid carcinomas of this structure by clinical appearance alone.

In the present series adenoid tumors occurred with slightly greater frequency in the hard palate (11 cases, 57 per cent) than in the soft (8 cases, 43 per cent); in 4 cases the growth appeared to arise at the junction between the two. Theoretically this proportion should be reversed, since the racemose mucous glands are more numerous in the soft palate than in the hard. The relative proportion of adenocarcinomas

and mixed tumors was about the same in all parts of the palate. Since these tumors always grow slowly, there has been adequate opportunity in the Head and Neck Clinic of the Memorial Hospital to observe them in all stages of development. In some cases they may be diagnosed and treated while only 5 to 6 mm. in diameter. In the earlier stages both adenocarcinomas and mixed tumors of the palate appear as nonulcerated, nontender, sharply delimited rounded or ovoid submucous masses which produce a smooth bulge from the mucous surface and resemble such benign lesions as retention cysts. The mucosa overlying the small or moderate-sized lesions always appears normal.

From the standpoint of morbid anatomy, adenoid tumors possess a smooth contour and a sharply delimited border and in most cases have a definite capsule, at least until they have reached a diameter of 2 to 3 cm. The more malignant adenocarcinomas, however, tend to exhibit invasive tendencies more often than benign mixed tumors.

In the hard palate adenoid tumors, even adenocarcinomas, do not ordinarily produce perforation of the bone early in the course of the disease. When perforation occurs, it appears to be due more to erosion by pressure than to actual invasion of the bone as in epidermoid carcinoma. As the ovoid tumor enlarges in the soft palate, it tends to form a diffuse bulge on the lower surface, which may also extend to the upper.

Adenoid tumors, even though large, rarely produce ulceration of the mucous membrane. In the present series an adenocarcinoma ulcerated to the mucous membrane in only 1 of 16 cases, and in that instance the ulceration may have been due to the implantation of radon seeds at another clinic before the patient's admission to the Memorial Hospital. Ulceration was observed in 2 cases of benign mixed tumor; in one the growth had been present for twenty-five years; in the other the ulceration was due to a recurrence of the growth in the operative scar after incomplete removal at another hospital.

The growth of adenocarcinoma appears to be more rapid (average duration in the present series three years) than that of mixed tumor (average duration over five years), but both varieties may be of exceptionally long duration. In the present series 1 mixed tumor, 5 cm. in diameter, had been present for about twenty-five years, and 1 adenocarcinoma, 7 cm. in diameter, had been present for fifteen years. It is possible that the long duration of the latter was due to the fact that a benign mixed tumor had undergone more recent malignant degeneration. The shortest alleged duration was one week in the case of a mixed tumor, but since the lesion was 2 cm. in diameter it had obviously been present over a much longer period. New and Childrey⁴ reported an average duration of about four and a half years for adenocarcinoma and Ahlbom⁵ a duration of about six years for all mucous and salivary gland

tumors. The latter made the definite statement that there is little difference in duration of symptoms between the malignant and benign types; this does not agree with observations of palatal salivary gland tumors at the Memorial Hospital.

In brief, the most important clinical characteristics of adenoid tumors of the palate, both mixed tumors and adenocarcinomas, are, first, a slow rate of growth and, second, a noninfiltrative, encapsulated character. The growth of adenocarcinoma tends to follow a benign course for a long time, the local lesion resembling a benign mixed tumor and causing few if any symptoms. If the tumor is left uncontrolled, death seldom results from complications of the primary lesion but almost always is due to generalized metastasis. The shortest duration of life in any of the cases of unsuccessfully treated adenocarcinoma in this series was one year; death occurred as the result of complications of treatment. Excluding this case, the average duration of life in the fatal cases was about six and a half years.

The average duration of life from the onset of symptoms in the fatal cases of epidermoid carcinoma was one and a half years; in fatal cases of adenocarcinoma it was five years. There should be little difficulty in the local control of either malignant or benign mucous and salivary gland tumors of the palate. The small or even the fairly large tumors are sufficiently delimited and accessible in the palate to permit complete surgical removal, and it is only when these growths have deeply infiltrated the lateral pharyngeal walls or extended onto the base of the tongue that they become inoperable. Abshier³ and Goldsmith and Ireland¹² mentioned the tendency of mixed tumors in the palate to recur locally, which seems to me to indicate an unnecessarily incomplete removal. Rhoads and Mecray,⁷ on the other hand, stated that recurrences of mixed tumors are extremely rare. In the palate the mucous and salivary gland tumors are almost invariably single, and recurrences can be due only to incomplete removal. In the parotid gland, although recurrences should still be rare, the possibility is greater, even after surgical removal, for it is well known that mixed tumors may be multiple and that adenocarcinomas tend to infiltrate the gland substance at an earlier stage. In Ahlbom's report, so far as I can determine, there is no definite statement as to the number of recurrences following surgical removal of salivary gland tumors of the palate.

Metastases.—In the present series metastases were demonstrated clinically in 45 per cent of the patients with malignant tumors on admission and developed later in an additional 16 per cent, so that in 61 per cent metastases were present at some time during the course of the

12. Goldsmith, P. G., and Ireland, P. E.: Mixed Tumors in the Nose and Throat, *Ann. Otol., Rhin. & Laryng.* 45:940, 1936.

disease. This figure is about the same as that for patients with cancer of the tongue and of the cheek, but it is less than that for patients with cancer of the nasopharynx and of the tonsil. If the lesions are separated into those which arise definitely in the hard and those which arise in the soft palate, excluding those at the junction of the two palates, it is apparent from the present series that malignant growths of the soft palate are much more likely to metastasize (72 per cent) than those of the hard palate (42 per cent). The comparatively high incidence of metastases from tumors of the soft palate may probably be accounted for by the mobility of this structure, which favors the detachment of tumor emboli. The converse is true of the fixed hard palate.

In the present series, epidermoid carcinoma appeared much more likely to metastasize (69 per cent of the cases) than adenocarcinoma (27 per cent), but a preponderance of metastases from the soft palate was common to both histologic forms of growth. New and Childrey⁴ made the rather ambiguous statement that about 16 per cent of the patients with adenocarcinoma of the palate had "enlarged cervical nodes", but they gave no information as to any subsequent clinical or histologic confirmation in their cases.

The lymph nodes most frequently involved first were the subdiaphragic (upper deep cervical) nodes of the internal jugular chain (in 72 per cent of the cases with metastases). The lymph nodes involved next in order of frequency were the prevascular or retrovascular nodes of the submaxillary group (16 per cent). After involvement of these nodes, the disease progressed in order to the middle and inferior nodes of the internal jugular chain. It is well known that adenocarcinoma of the oral cavity or of the skin of the head and neck may metastasize systemically without involvement of the intervening lymph nodes. In Watson's series of patients with intraoral adenocarcinoma from the Memorial Hospital, 10 had systemic metastases and only 5 (50 per cent) of these had metastases to the cervical lymph nodes. Of patients with palatal adenocarcinoma in the present series, 2 had systemic metastases but neither had involvement of the cervical lymph nodes.

Systemic Metastases.—In the autopsy records¹³ of the Memorial Hospital there are 8 cases of patients who died of epidermoid carcinoma of the palate, and in 1 of these there were systemic metastases to the following sites: liver, peritoneum, bladder, adrenals, myocardium, skeletal system, skeletal muscles, lungs, skin and choroid plexus. There are also 3 cases of patients who died of adenocarcinoma of the palate, and in 2 of these there were systemic metastases.

13. Braund, R. R., and Martin, H. E.: Distant Metastases in Cancer of the Upper Respiratory and Alimentary Tracts, Surg., Gynec. & Obst. **73**:63, 1941.

HISTOPATHOLOGY

The histologic distribution of the palatal neoplasms in the present series is given in table 2. Benign tumors (of salivary gland origin) comprise about 7 per cent of the series and malignant tumors (epidermoid and adenocarcinoma) about 93 per cent. Of the malignant tumors, epidermoid carcinoma makes up about 83 per cent and adenocarcinoma about 17 per cent. There were in addition 1 melanoma and 1 rhabdomyosarcoma. Lymphosarcoma occasionally arises in the palate, although there was none in this location in the present series. Benign leiomyosarcoma has been reported as occurring in this area, but none so situated is on record at the Memorial Hospital.

From the histologic standpoint epidermoid carcinoma of the palate does not differ materially from epidermoid carcinoma of other regions of the oral mucous membranes; hence this subject requires no detailed

TABLE 2—*Histologic Distribution of Palatal Tumors Observed at Memorial Hospital*

I Epidermoid tumors .		74
Squamous cell ..	67	
Transitional cell	6	
Melanoma . .	1	
II Glandular tumors ..		24
Adenocarcinoma .	16	
Mixed tumors of salivary gland type	8	
III. Mesodermal tumors .		1
Rhabdomyosarcoma	1	
Total ..		99 *

* In the remaining 2 cases the patients were referred for treatment of metastases, there was no disease in the primary site.

analysis in this report. In the present series there were 6 transitional cell carcinomas, 3 in the soft palate and 3 in the hard.

Adenoid tumors (adenocarcinomas and benign mixed tumors) comprise about 23 per cent of all palatal tumors. These glandular tumors of the palate are presumably derived from minor salivary and mucous glands of the oral mucosa and show every variety of structure seen in the major salivary glands. Tumors resembling those arising in minor salivary glands are occasionally encountered beyond the limits of the oral cavity—in the esophagus, in the subglottic region, in the lower part of the trachea, in the primary bronchi, where they presumably arise from mucous glands, and in the nasal cavity. The sweat glands occasionally produce tumors indistinguishable from salivary gland mixed tumors. So also, rarely, does the breast, especially in dogs. In all of these areas tumors varying in structure from adenocarcinoma to a relatively benign mixed cystic structure may arise.

The theories held by some that these adenoid tumors arise from embryonic rests, from misplaced remnants of the salivary glands or from

branchial pouches are, it seems to me, superfluous. In the first place, these tumors occur frequently outside the areas of the branchial pouches. In the second place, the normal mucosa, where these tumors arise, contains glandular structures (racemose and mucous), and the relative incidence of these tumors in various sites corresponds closely to the relative abundance of minor salivary glands in the mucosa. For example, their incidence in the palate, the base of the tongue and the tonsillar pillars, structures which contain a relatively large number of minor salivary and mucous glands, is much greater than their incidence in the lip, the anterior portion of the tongue, the mucosa of the cheek and the nasopharynx, where there are relatively few of these glands. In the nasal cavity, where the mucous glands are numerous, a bizarre variety of neoplasms arise, a large proportion of which have adenoid elements, although they do not follow closely the characteristics of palatal adenoid tumors.

The literature on the classification of salivary and mucous gland tumors, both of the major and of the minor salivary glands, is extremely complex and confusing, especially since there is a tendency to combine morphologic and embryologic distinctions in the same classification. Ahlbom,⁵ after reviewing the literature and rejecting most of the newer concepts, returned to the more simple classification of Masson and Peyron¹⁴; that is, he separated these tumors into benign mixed tumors, semimalignant mixed tumors and malignant tumors (adenocarcinoma). It is my opinion that any attempt at a clear classification of these growths is artificial, since there is probably a gradual transition from the definitely benign mixed tumors through the increasing degree of cellularity of the intermediate grades to the other extreme of highly malignant adenocarcinomas. The designation by some authors of a semimalignant group is obviously either a frank or an unwitting admission of this gradual transition or intermediate stage in which the exact diagnosis is uncertain. Finally, as opposed to a clear classification into definite groups, it can be stated with certainty that the histologic and clinical character does not remain fixed within an individual tumor and that a growth which begins as a benign mixed tumor may, after a varying period, undergo malignant degeneration, so that eventually the clinical course may progress to a rapid termination with a widely metastasizing adenocarcinoma.¹⁵

14. Masson and Peyron: *A propos des tumeurs mixtes des glandes salivaires. Spécificité cellulaire et tumeurs mixtes*, Bull. Assoc. franç. p. l'étude du cancer 7:219, 1914.

15. An example of malignant degeneration of a benign mixed tumor is found in the following case: A doctor first noted a subcutaneous tumor in his parotid region about 1910. The growth was excised after having been diagnosed as a benign mixed tumor; the diagnosis was proved to be correct on histologic exami-

Dr. Fred Stewart, pathologist at the Memorial Hospital, has reviewed the histologic material included in this report and makes the following comments on the histogenesis of mucous and minor salivary gland tumors:

The "mixed" tumors reveal a complex histologic structure, consisting of epithelial elements in the form of strands, masses, tubules or alveoli, together with mucoid pseudomesenchymal tissue and cartilage. Any of these elements may predominate to produce the appearance of a pure structure, such, for example, as chondroma or myxoma. Most pathologists now accept the purely epithelial origin of the cells and regard the mucoid tissue, spindle cell areas and cartilage as metaplastic in nature; hence they employ the term "mixed tumor" to describe structure rather than to imply complex origin. The purely epithelial origin of these lesions was clearly recognized by Krompecher¹⁶ and has gained wide credence.

The frankly carcinomatous tumors of minor salivary glands are of several types and presumably of several origins, although the average tumor when first seen is too advanced to enable one to decide its exact origin definitely. Carcinomas are more or less divisible according to distinct morphologic patterns but frequently reveal transition pictures making it difficult to place them in single categories. Thus, in a "mixed" tumor differences in size and shape of cells, nuclear variability and hyperchromatism enable one to predict or suspect an eventual recurring malignant clinical course. The lesion recurs and metastasizes as alveolar carcinoma, rarely as a malignant "mixed" tumor of complex structure.

Certain tumors which pursue a malignant course are best designated as cylindromas from their resemblance to basal cell tumors of the skin. Others resemble the common adenoid basal cell tumors of the skin and show solid cords of epithelial cells interrupted by glandlike spaces or small cysts. These have been designated as adenoid cystic adenocarcinomas. When they arise in a mucous membrane derivative they are uniformly malignant and may metastasize as widely as any known type of tumor—to nodes, serous membranes, thoracic and abdominal (and even pelvic) viscera and bones. Occasionally the mucoid pseudomesenchymal element of a mixed tumor yields metastases which resemble the structure of pure myxosarcoma. Mixed tumors or pure carcinomas may exhibit epidermoid or squamous areas, either as a form of metaplasia or because a duct element is present. Thus the picture of squamous carcinoma arises. Pure solid or small alveolar carcinomas are rarely encountered; they run a malignant course.

Rarely in the oral cavity one finds pure mucous gland cancer of papillary or alveolar structure resembling cancer of the stomach or of the lower gastrointestinal

nation. The growth recurred after a few years. About eight or nine years later it was again excised and again found to be a benign mixed tumor. About 1925 there was a further recurrence, followed by a third excision, but at that time the growth histologically was adenocarcinoma. A fourth recurrence took place, and the patient was seen at the Memorial Hospital with a typical deeply invading postoperative adenocarcinoma of the parotid gland. He finally died of local recurrence and disseminated cancer. The slides of the earlier operation were all reviewed by Dr. Fred Stewart at the Memorial Hospital, who found the tissue removed at the first two operations to be clearly representative of benign mixed tumor, whereas the later specimens were representative of adenocarcinoma.

16. Krompecher, E.: Zur Histogenese und Morphologie der Mischgeschwülste der Haut sowie der Speichel- und Schleimdrüsen, Beitr. z. path. Anat. u. z. allg. Path. 44:51, 1908.

tract and indistinguishable microscopically from such tumors. A peculiar clear cell cancer of minor salivary gland origin or of mucous gland origin may be indistinguishable from metastatic renal clear cell cancer.

The only absolute criterion of malignancy of salivary or mucous gland tumors is their capacity to metastasize. Eggers¹⁷ and others have perhaps overemphasized perforation of the capsule as a malignant characteristic of these tumors. While it is conceded that perforation of the capsule and local infiltration are often a characteristic of tumors which metastasize, it must be admitted that such local invasion without metastasis does not by itself render a given tumor malignant. Even the most malignant metastasizing salivary and mucous gland tumors may remain encapsulated but nevertheless metastasize widely. Furthermore, post-operative recurrences of benign mixed tumors may infiltrate the local tissues.

Melanoma, which occurs more commonly on the gums than in any other part of the oral cavity, occurs next in frequency on adjacent structures, namely, the hard palate and the mucosa of the cheeks. In the present series there was 1 case of melanoma, in a man 65 years of age, who died, after two years of generalized metastases. There was also 1 case of rhabdomyosarcoma, in a child of 8 years. The growth was moderately radiosensitive but recurred locally and finally metastasized to the lungs; the patient died after fifteen months. There was another case of rhabdomyosarcoma, more recent than the present series. The tumor originated in the soft palate; it recurred repeatedly after removal by cautery, but was finally controlled locally. At the time of writing the patient has survived without recurrence for two years since the last treatment.

DIAGNOSIS

Several varieties of benign lesions and tumors occur in the palate and may at times present problems in differential diagnosis. The benign nature of some of these lesions, such as torus palatinus and dentigerous cyst, should be immediately apparent on clinical examination alone. With others, especially when there is ulceration, a confirmation of the diagnosis should be made by biopsy prior to the institution of the necessarily aggressive treatment for cancer, either surgical or radiologic. In the case of a superficially ulcerated lesion a specimen for biopsy is readily removed. In the case of a nonulcerated submucous tumor, incision through intact mucous membrane for the removal of a specimen is highly objectionable, since the maintenance of an intact capsule is of paramount importance in the complete surgical removal. I do not believe that surgical biopsy can be the direct cause of malignant

17. Eggers, H. E.: Mixed Tumors of the Palate, *Arch. Path.* 6:378 (Sept.) 1928.

transformation of a benign mixed tumor. The risk of permitting a tumor to spill outside its capsule, thus making its subsequent removal more difficult or increasing the chance of metastasis, is sufficient argument against surgical biopsy of these tumors.

In cases of these nonulcerated tumors aspiration biopsy finds one of its most definite indications. From the aspirated specimen it is not always possible to differentiate between benign mixed tumor and adenocarcinoma, but this point is of only minor importance since the treatment, surgical removal, is the same in either case and the exact histologic classification can safely await the microscopic examination of excised tumor.

Cancer of the antrum may invade the bony antral floor, and the growth, under pressure in the antral cavity, may then produce a bulge of the palate without perforating the mucous membrane. This bulge may be mistaken for an adenoid tumor of the palate. The differential diagnosis can ordinarily be made by roentgenographic examination, which demonstrates an opacity of the antral cavity and destruction of its other bony walls. Such an antral growth is also likely to be found invading the nasal cavity. The diagnosis may be confirmed by aspiration biopsy of the antral cavity either through the palate or through the cheek. If epidermoid carcinoma is found on aspiration biopsy of a nonulcerated bulging tumor of the hard palate, the diagnosis of antral rather than palatal cancer is almost certain.

Delay in Diagnosis.—As might be expected, diagnosis of the slowly growing adenoid tumors is delayed longer (thirty-five months from the beginning of symptoms) than that of the epidermoid growths (seven months). When medical advice is first sought, the diagnosis is missed in about 25 per cent of the cases of both the adenoid and the epidermoid tumors, and the patients are given some form of local treatment, such as mouth washes or topical applications, or they are assured that the lesion is of no particular significance. As in most cases in which the physician or the dentist fails to recognize cancer when he first sees it, the fault arises both because of unfamiliarity with the appearance of cancer and because of failure to recognize the importance to the patient of immediate diagnosis and treatment.

Differential Diagnosis.—Benign lesions which may be confused with neoplasms of the palate will be discussed separately.

(a) *Granuloma or Simple Ulcer:* During the period covered by the present report, 17 patients with granuloma or nonspecific ulcer applied or were referred for a differential diagnosis of cancer—about one sixth as many as the whole group of patients with cancer. Such benign lesions are not uncommonly observed in the midline of the hard palate in heavy smokers, and they cannot be differentiated clinically from cancer. The correct diagnosis is made by biopsy.

(b) *Papilloma*: As in all parts of the oral mucous membrane, in the palate the neoplastic response to chronic irritation may take the form of papilloma rather than of carcinoma. In the hard palate such a lesion usually occurs near the midline and may in rare instances spread over considerable areas of the palate. In the soft palate it occurs as papillary warty projections, which the experienced observer can diagnose clinically. Eleven patients with papilloma were admitted to the hospital during the period of the present report (one tenth as many as the patients with carcinoma). The treatment is preferably by strictly local removal with the actual cautery. Radiation therapy should not be used for these benign epithelial growths of the palate.

(c) *Torus Palatinus*: This lesion is an osteoma which occurs at about the center of the hard palate where the two maxillas are fused in the midline. If careful examinations are made, a slight prominence at this point is found in a high percentage of otherwise normal adults. In some persons the lesion takes on greater growth and forms a hard, fixed, smooth or nodular prominence, 2 to 4 cm. in diameter, covered by normal mucous membrane. Its true character—that is, solid bone overlaid by normal mucous membrane—is fairly obvious on close examination. The lesion has no significance except that in some instances it interferes with the proper fit of a dental plate. If so desired, the bony tumor may be removed by a chisel and the base left to heal by granulation and epithelization from the borders. Seven patients with torus palatinus applied to the Memorial Hospital during the period covered by the present report.

(d) *Syphilis*: Gumma of the oral mucous membrane cannot be distinguished clinically from cancer, but it is extremely rare. No gumma of the palate was encountered during the period covered by the present report, although since this series was collected 2 such lesions have been observed, both proved to be gumma by biopsy, which was negative for cancer, positive Wassermann tests and a therapeutic test (that is, they disappeared under antisyphilitic treatment).

(e) *Dentigerous Cyst or Adamantinoma*: Either a benign dentigerous cyst or an adamantinoma of the upper jaw may produce a smooth rounded cyst of the palate which can be mistaken for an adenoid tumor. The diagnosis should be made by roentgenographic studies and aspiration biopsy. A correct diagnosis is important from the standpoint of treatment. A dentigerous cyst should be opened widely and drained, and the cyst wall left as the epithelial covering of part of the defect. Adamantinoma of the upper jaw always originates within the bony structure, and although it occasionally produces a bulge on the hard palate, it will be found on closer examination to have an even wider extent in the other portions of the maxilla. The surgical removal of an

adamantinoma necessitates much wider excision of bone than the removal of an adenoid tumor or of a dentigerous cyst arising in the hard palate.

TREATMENT OF THE PRIMARY LESION IN CANCER OF THE PALATE

The selection of the method of treatment of a palatal tumor depends both on the histologic variety and the site of the tumor (hard or soft palate). In general the adenoid growths, both mixed tumors and adenocarcinomas, are radioresistant. There seems to be little difference between the two, although adenocarcinoma may occasionally be moderately more radiosensitive. To be cancer lethal, the dose of radiation for these adenoid tumors must be large enough to produce radionecrosis in almost all cases. Even then it may still fail to sterilize all parts of the tumor, and the chance of local recurrence is high. In contradistinction to the superficial eroding indefinitely outlined epidermoid carcinomas of mucous membrane, these submucosal adenoid growths tend to be globular or ovoid with sharply delimited borders and sometimes with a definite capsule. The latter characteristics of adenoid tumors coupled with their high radioresistance makes them more suitable to surgical removal than to radiation treatment.

Mild preoperative or postoperative irradiation of these radioresistant tumors is illogical. Most authors have favored surgical excision rather than irradiation of these adenoid tumors, but with the exception of Abshier³ they have recommended either preoperative or postoperative irradiation. Ahlbom⁵ expressed the belief that treatment should always begin with fractionated external irradiation except for the clearly benign mixed tumors. After irradiation he recommended electrosurgery and then postoperative irradiation. Some authors¹⁸ have recommended postoperative irradiation in all cases, usually by placing radium in the wound cavity.

It seems to me that such preoperative and postoperative irradiation of these highly radioresistant, operable benign and malignant salivary gland tumors of the palate is illogical. If, as is possible in most cases, the tumor has been completely removed, irradiation can be of no benefit and only retards healing. If a portion of the tumor has been left, the application of sublethal doses of radiation can be of no benefit, and cancer-lethal irradiation of recurrent nodules must be so aggressive as to be unsafe except in a very limited volume of tissue. In my opinion mild preoperative and postoperative irradiation of cancer is an arbitrary

18. Bland-Sutton, J.: *Tumours, Innocent and Malignant*, ed. 7, London, Cassell & Co., 1922, p. 414. Hill, F. T.: *Mixed Tumors of the Hard Palate*, *Ann. Otol., Rhin. & Laryng.* 47:317, 1938. Seltz, S.: *A Case of Adenosarcoma of the Palate*, *J. Med.* 17:87, 1936. Ahlbom.⁵ Goldsmith and Ireland.¹²

custom which has persisted in many clinics from the days when the action of radiation on malignant tumors was not well understood and when it was believed that mild irradiation of cancer was always of benefit to the patient even though it produced no visible effect on the growth. The application of mild doses of radiation over large volumes of tissue is not without its harmful constitutional effects.

Epidermoid carcinoma of the palate exhibits about the same radiosensitivity as other epidermoid growths of the oral cavity. These epidermoid tumors in the soft palate tend to be highly radiosensitive, as are the adjacent pharyngeal growths (in the tonsil, base of tongue, extrinsic larynx, etc.). In the soft palate particularly, epidermoid carcinomas infiltrate early and irregularly, making wide surgical removal difficult in a structure which is functionally important and where defects are almost impossible to repair surgically or even mechanically by prosthetic appliances. The chance of curing epidermoid carcinoma of the soft palate is much greater by irradiation than surgical removal.

In the hard palate an epidermoid carcinoma arising in the thin layer (2 to 3 mm.) of soft tissues overlying bone is in immediate contact with bone, or at least with periosteum, in all cases. Application of cancer-lethal doses of irradiation to such a growth always considerably devitalizes the underlying bone and often results in the exposure of the heavily irradiated bone, with inevitable radio-osteomyelitis and a long period of morbidity, until sequestration has taken place. For this reason, surgical removal of epidermoid carcinoma of the hard palate by cautery and chisel is often preferable to radiation therapy.

In brief, the treatment of adenocarcinoma and of mixed tumors of the hard or the soft palate is preferably by surgical removal. Epidermoid carcinoma of the hard palate is usually best treated by surgical removal, though occasionally radiation therapy or combinations of radiation therapy and surgical removal are indicated. For epidermoid carcinoma of the soft palate radiation therapy is almost always the method of choice.

The technics of treatment for the various areas of the palate will be described under separate headings and in the legends which accompany the illustrations.

Surgical Removal of Palatal Tumors.—The most efficient instrument for the surgical excision of palatal tumors is the actual cautery, with the assistance of a chisel for the removal of underlying bone in the hard palate. For a tumor of the hard palate, a moderate-sized, red-hot cautery loop should be used to cut through the soft tissues down to the bone, the line of excision including a safely wide margin (5 to 10 mm.) of normal tissue at the border of the growth (fig. 2 *A*). After preliminary incision of the overlying soft parts by cautery, the underlying bone is cut through with a bone chisel, the lesion removed, and the projecting spicules of bone smoothed down with a rongeur (fig.

2B and C). Such a procedure always includes opening and removal of the floor of the antral cavity or of the nasal cavity or of both. The wound should be packed immediately to prevent hemorrhage. Bone wax may be used to plug larger spurting vessels emerging from the bone. In some instances of mixed tumor or adenocarcinoma of the hard palate, it may be safe to strip the capsule and the periosteum from the bone without making a perforation (figs. 3 and 4). The judgment of the surgeon must determine whether or not such a conservative plan is justified from the standpoint of safety in the individual case. In the

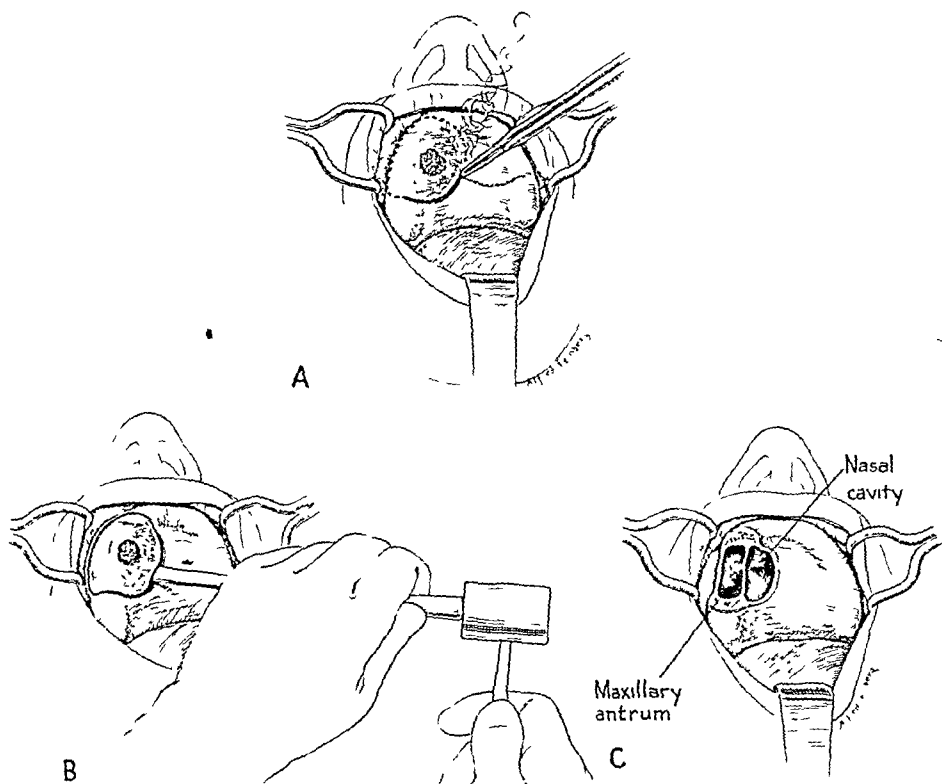


Fig. 2.—Surgical excision of a palatal tumor by cauterization and chisel. *A*, the growth is circumscribed by cutting through the soft tissues overlying the palate and the alveolar process with a fine-bladed actual cautery. *B*, with a sharp chisel and a mallet the bone underlying the tumor is mobilized. *C*, the tumor with the underlying bone is removed, exposing the maxillary antrum and the nasal cavity.

case of epidermoid carcinoma of the hard palate, underlying bone should always be removed.

In the soft palate only the adenoid tumors should be treated by cautery removal, and an effort should be made in all cases to avoid through and through perforation of the structure if at all possible. A finer caliber cautery loop should be employed in the soft palate than in the hard. An area of the overlying mucous membrane should be

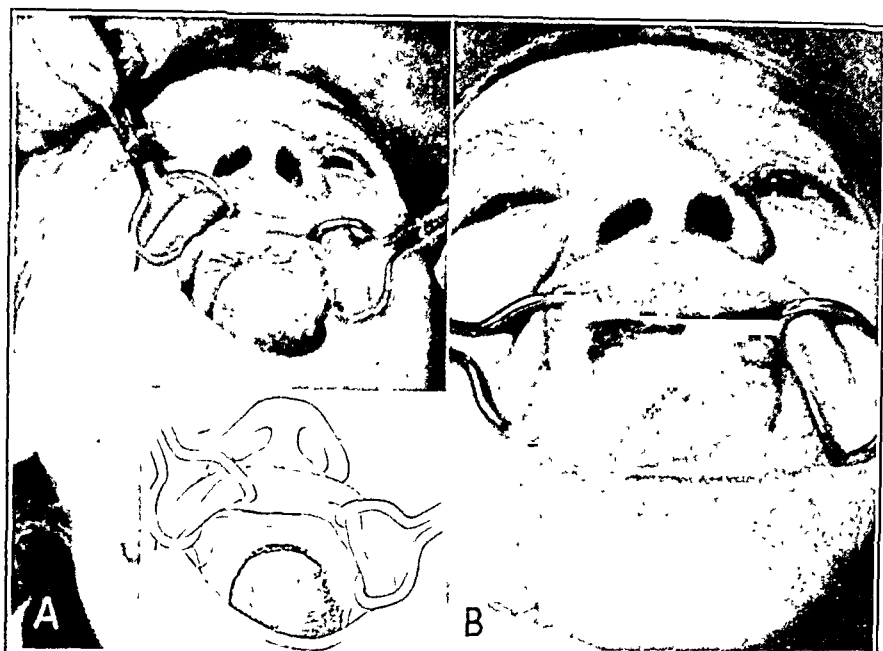


Fig. 3.—M. G., a woman aged 67, was admitted to the hospital April 17, 1936, with a swelling of the palate of fifteen years' duration. There was a bulging, ulcerated, slightly fluctuant tumor covering almost the entire hard palate (A). The insert shows the extent of the tumor. Physical examination and roentgenographic study indicated that the bone of the palate had not been invaded by the growth. The tumor was excised by cautery and periosteal elevator without removal of any bone. Histologic examination showed a mixed tumor of the salivary gland type. Healing took place by secondary intention, and there has been no recurrence in the palate after five years (B).

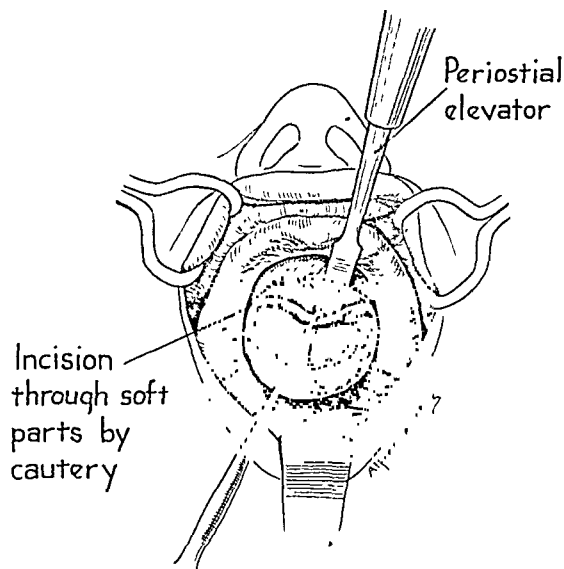


Fig. 4.—Surgical excision of relatively benign cystic tumor of the palate which does not invade bone. The tumor is circumscribed by an incision with the actual cautery as shown in figure 2A. The growth is then mobilized from the hard palate by blunt dissection with a periosteal elevator.

removed with the tumor. A useful point in the technic is the placement of one or two silk or dermal sutures in the mucous membrane and the capsule near the center of the tumor to produce immobilization and some traction on the growth which would otherwise tend to be depressed into the palate, so as to obscure the intended line of incision. By working slowly, guided by digital palpation, an extracapsular dissection by the cautery is carried out, and by clamping and tying a few moderately sized blood vessels the procedure in many instances can be kept practically bloodless. The wound is left open to heal by granulation except in the case of a small tumor, in which one or two sutures may be used to close the incision loosely.

In the expansile growth of the larger adenoid tumors of the soft palate, especially those which arise near the free border, there may be deep fixation in the tonsillar region; in the treatment of such a tumor the cautery can be used only at the beginning of the operation. When the apex of the tumor has been freed, the rest of the operation must be carried out mainly by blunt dissection and by enucleation with the fingers. When such a larger tumor is situated laterally, the operation had best be preceded by ligation of the external carotid artery on the involved side. There is a consistent tendency of all adenoid tumors of the palate and of the tonsillar region to remain sharply delimited and noninfiltrating, so that even for the larger growths (5 to 6 cm. in diameter) the possibility of complete removal by enucleation should always be considered. Unless the surgeon is fully conversant with the morbid anatomy of these adenoid tumors, he is likely to overlook the fair possibility of permanent control by surgical removal and to consign the patients at once to radiation therapy, which offers little or nothing, even from the standpoint of palliation, with these bulky, radioresistant growths.

In the present series, 2 adenocarcinomas were treated by surgical excision alone (fig. 5), 2 by a combination of irradiation and surgical removal (fig. 6) and 2 by irradiation alone. Of the 4 successfully treated epidermoid carcinomas of the hard palate, 2 were treated by a combination of irradiation and surgical removal and 2 by surgical removal alone.

Combinations of Irradiation and Surgical Removal in the Treatment of Palatal Tumors.—Surgical removal of a residual or a recurrent palatal tumor after radiation therapy is sometimes indicated, or it may be of advantage to remove an area of devitalized or radionecrotic soft tissue and bone after complete destruction of the growth by irradiation.

Formerly at the Memorial Hospital many adenocarcinomas were treated by heavy interstitial irradiation and cautery removal after a week to ten days. The rationale of such a procedure was that there would be a cancer-lethal radiation effect at the line of excision, so that

the chance of recurrence would be much reduced. In view of the high radioresistance of these adenoid tumors as well as of their sharp delimitation it is probable that such a combination of irradiation and surgical treatment is not superior to surgical removal alone. Although in our series such combinations were successful in several instances, it is significant that there were no recurrences following simple surgical removal even when the irradiation was omitted.

Radiation Treatment of Palatal Tumors.—As has been mentioned previously, irradiation should not be used for adenoid tumors of the palate if there is a chance of their surgical removal. In the hard palate

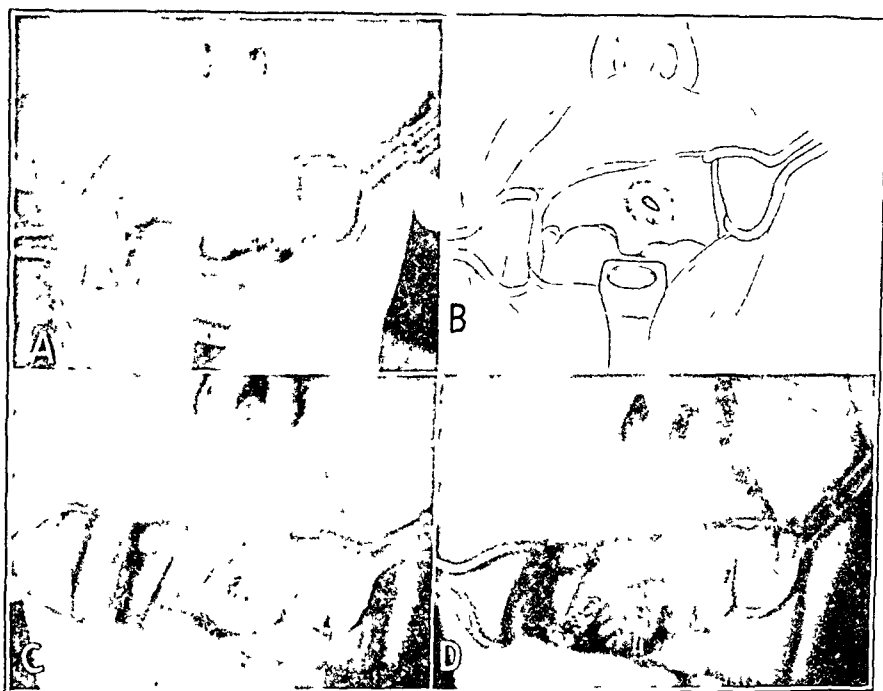


Fig. 5.—G. B., a man aged 61, was admitted to the hospital Dec. 8, 1936, with a diagnosis of adenocarcinoma of the palate. The primary lesion in the left soft palate crossed the midline (*A* and *B*). The growth, 2 cm. in diameter, originally nonulcerated, had been incised for biopsy before admission. The lesion was removed by the fine loop of an actual cautery with the region under local anesthesia (*C*). Healing took place by secondary intention, and the growth has not recurred (*D*). After an irregular follow-up, bilateral cervical metastases were discovered two and a half years later. Bilateral neck dissection was performed in two stages with an interval of two months between the operations, the internal jugular vein being removed only on the left side. Histologic examination showed metastatic invasion of lymph nodes on both sides. After these neck dissections the patient has remained well for two years.

even epidermoid carcinomas are not always best suited to radiation therapy. The selection of the exact method of treatment is often optional and may depend on the facilities available and on the experience and

ability of the individual surgeon with the various methods. If irradiation is used for a tumor in the hard palate, the technic is similar to that for a tumor in the soft palate, which is as follows:

In irradiating palatal tumors an attempt should be made to rely mainly on roentgen radiation given perorally, so as to spare the soft tissues of the cheeks and the parotid salivary glands. If a palatal growth is so large or extends so far down the lateral pharyngeal wall that the largest preoral portal does not include all of the lesion, additional treatment must be given through the skin of the cheeks. The smaller or

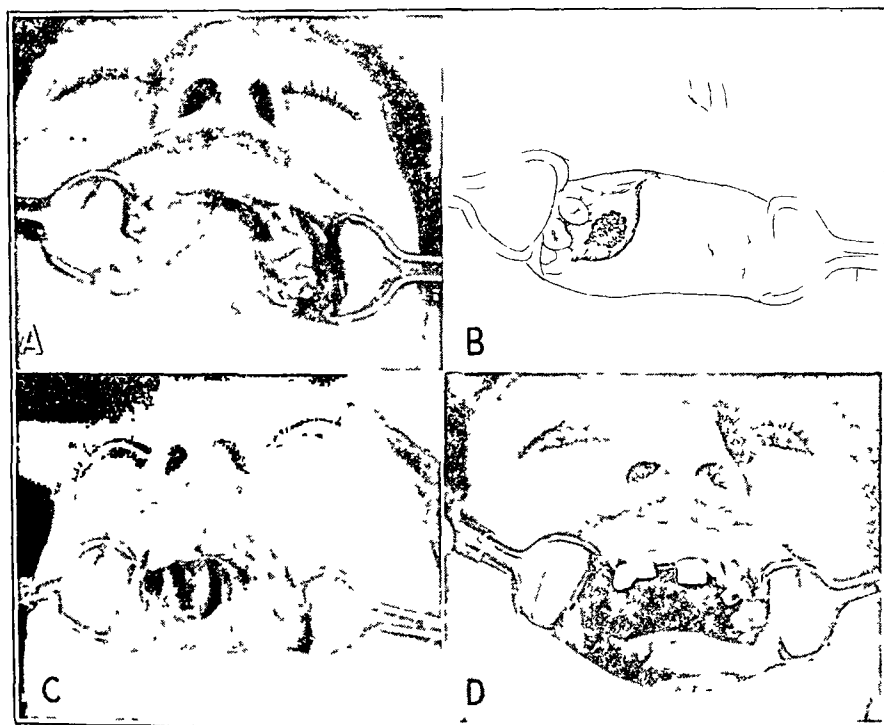


Fig. 6.—C. A., a man aged 28, was admitted to the hospital Sept 11, 1936, with a history of a swelling in the right side of the hard palate of four years' duration. Examination revealed a diffuse firm swelling of the right side of the hard palate 3 cm. in diameter with an area of ulceration 1.5 cm. in diameter (A and B). Histologic examination showed a mixed tumor of salivary gland type which was becoming carcinomatous. The lesion appeared to be definitely attached to the bone, if not invading it. The growth was treated by radon gold seeds (21 millicuries) followed in one week by wide excision with chisel and cautery. Healing took place with a large defect in the right side of the hard palate (C). The defect was closed by a prosthesis which completely restored normal speech and relieved disability in swallowing. The patient has remained well for five years (D).

average-sized palatal growths (up to 3 to 4 cm. in diameter) can be approached perorally, using cylinders between 3.5 and 4.5 cm. in diameter, accurately centered with a lighted periscope, as described in

previous publications.¹⁹ A daily dose of 300 to 400 r is given for a total of 7,000 to 8,000 r with high voltage (200 to 250 kilovolts) radiation or 12,000 to 14,000 r if low voltage (100 to 120 kilovolts) should be used. When the growths are on the surface, the shortest practical target-skin distance (15 to 25 cm.) should be employed. If external portals are used in addition to the peroral, these should be directed through the skin of the cheeks, the exact centering being carefully determined and marked on the skin, preferably by a small tattoo mark.²⁰ The external portals may be 6 to 7 cm. in diameter. With the use of such multiple portals, the individual and total doses are variable and empiric.

After the external irradiation, depending on the response of the lesion, it is usually of advantage to apply a supplementary dose of radon seeds interstitially. In most cases such supplementary interstitial irradiation is preferable to an attempt to control the disease entirely by external irradiation. The dose of seeds is somewhat empiric and varies widely in the individual case. The individual strength of the radon seeds should be about 1.5 millicuries. For growths of the hard palate, dependence must be placed mainly on external (peroral) irradiation, since the thin layer of soft tissue overlying the bone is usually not great enough to permit retention of interstitial implants. This is one of the reasons why external irradiation is not so successful in the hard as in the soft palate. The largest successful dose of radon seeds used in combination with external irradiation in the treatment of epidermoid carcinoma of the soft palate in the present series was 20 millicuries.

TREATMENT OF CERVICAL METASTASES FROM CANCER OF THE PALATE

In the Head and Neck Clinic at the Memorial Hospital the treatment of cervical metastases from epidermoid carcinoma of the palate does not differ from that of metastases from other forms of intraoral cancer.²¹ If no metastases are clinically demonstrable on admission, no

19. (a) Martin, H. E., and Sugarbaker, E. D.: *Cancer of the Tonsil*, Am. J. Surg. 52:158, 1941. (b) Martin, H. E.: *Variations in Radiation Technic and Biologic Effects in the Treatment of Pharyngeal Cancer*, Radiology 34:149, 1940.

20. The skin is cleansed with alcohol, and a small drop of india ink is placed at the selected point. With a sterile sharp-pointed surgical needle, several punctures are made through the india ink into the skin. Such a mark remains permanently, but its size can be so small as to be unobjectionable.

21. Few authors have mentioned the treatment of cervical metastases from palatal tumors except Ahlbom,⁵ who in a discussion of all mucous and salivary gland tumors recommended prophylactic irradiation of the cervical lymph nodes in all cases of malignant salivary gland tumor. It is difficult to see the logic of such a procedure, especially for these radioresistant tumors, as the radiation control of even the localized primary lesion can hardly be accomplished without producing radionecrosis. Ahlbom agreed with the policy of the Memorial Hospital of per-

treatment of any kind is given to the neck. If the primary lesion is controlled, the patient is kept under systematic observation, both for recurrence in the primary site and for metastasis to the neck, and treatment to the neck is given only if and when metastases develop. The soundness of such a policy of watchful waiting is based on the analysis of the clinical behavior of metastases from intraoral cancer in general and has been discussed repeatedly in previous reports from this clinic.

If there is palpable involvement of the cervical lymph nodes by epidermoid carcinoma on admission, the treatment in most cases should be by irradiation—fractionated roentgen radiation through small portals to the individual nodes, supplemented by implantation of radon seeds. The indication for radiologic rather than surgical treatment in these cases is that if metastases are present on admission the growth in the palate is almost invariably far advanced and suitable only to treatment by aggressive irradiation. Neck dissection in these cases cannot be performed in conjunction with the aggressive irradiation of the palatal growth and is therefore of little or no value in the treatment of metastatic nodes already present on admission.

The detailed technic of radiation therapy for metastatic cervical cancer has been described previously²² and will not be repeated here except in brief outline. The dosage is variable and depends on the size of the portal and the relation of the metastatic node to the primary lesion, and on the possibility of including the two within a single radiation beam. When metastatic nodes are treated through separate portals, 4 to 5 cm. in diameter, 7,000 to 8,000 r may be given over a period of three weeks (200 to 250 kilovolts, target-skin distance, 35 cm.; filter, 0.5 to 1 cm. of copper), supplemented by radon seeds (often given in fractions) in doses of 10 to 20 millicuries, depending on the size of the node. In the present series, 2 patients with metastases (proved by aspiration biopsy) were treated by irradiation alone and have survived five years without recurrence.

If metastases from epidermoid carcinoma of the palate occur at an interval after control of the primary lesion, the method of treatment is optional and may be either by irradiation or by neck dissection. The choice of neck dissection rather than of irradiation might be based somewhat on the position of the primary lesion and on whether the metastatic nodes are unilateral or bilateral. If such late metastases are

forming neck dissection only when cervical lymph nodes are palpably involved, but he recommended an attempt to obtain regression by irradiation of the involved nodes before resorting to surgical removal.

22. Martin, H. E.; Munster, H., and Sugarbaker, E. D.: *Cancer of the Tongue*, Arch. Surg. **41**:888 (Oct.) 1940. Martin and Sugarbaker.¹⁹⁴¹

bilateral or if the primary lesion was in the midline, indicating the possible development of bilateral nodes, the treatment should usually be radiologic rather than surgical. For late unilateral and homolateral metastases from a primary lesion not involving the midline, neck dissection is usually the preferable method and should be complete, extending down to the clavicle. In the present series neck dissection was successfully performed in 2 cases.

For cervical metastases from adenocarcinoma of the palate, which is always radioresistant, radiation therapy is not so useful as it is for epidermoid carcinoma. If the metastatic node is small (1 to 1.5 cm. in diameter), cancer-lethal radiation can be given without any particular difficulty by using a combination of external irradiation and a heavy dose of radon seeds. On the other hand, when metastatic nodes from adenocarcinoma are larger or multiple, the heavy cancer-lethal dose of radiation would have to be given over such large volumes of the neck as to make it highly objectionable or even dangerous. For these reasons neck dissection rather than radiation therapy is preferable in most cases of metastasis from adenocarcinoma, even though the operation must be bilateral.²³

23. A patient with adenocarcinoma of the soft palate treated five years ago and not cooperating in the regularity of his follow-up examinations was found to have bilateral metastases thirty-one months after excision of the primary lesion. Bilateral neck dissection was performed in two stages seven weeks apart. On one side the sternomastoid muscle and the internal jugular vein were removed. On the other side the vein was left in place, since it was felt that due to the patient's age (61 years) the removal of both internal jugular veins might be risky. It is probable, however, that the second vein could have been removed without any untoward result, because during a period of about half an hour near the close of the operation an assistant compressed the remaining internal jugular vein with his fingers and the patient seemed to suffer no marked ill effects, although during the compression the face became moderately cyanotic and venous bleeding from the upper portions of the wound was rather profuse. At the close of the operation the pressure was released. At the time of writing the patient has survived sixteen months without recurrence. The remaining internal jugular vein is still patent and at the present time may be occluded by digital pressure without any sign of venous congestion either in the cerebral cortex or in the subcutaneous tissues of the head.

There is little discussion in the literature as to either the safety or the advisability of removing both these vessels in bilateral neck dissection. Tailh  fer²⁴ stated that he had safely removed them in a few cases, with an interval of about a month between operations, but he does not consider it advisable as a rule. So far as I can learn, Crile has not mentioned it in any of his publications. In a personal discussion of this question, Jovin told me that one of his colleagues in Bucharest, Rumania, had removed both internal jugular veins in several cases without incident.

24. Tailh  fer, A.: Traitement chirurgical des ad  nopathies du cancer de la langue. R  sultats   loign  s, M  m. Acad. de chir. 62:975, 1936.

COMPLICATIONS

Pain.—Cancer of the palate is not a painful disease except in the advanced stages, when sepsis and necrosis occur in large volumes of heavily irradiated tissue. Intractable pain is likely to be a complication when persistent attempts are made to control the radioresistant mixed tumors or adenocarcinomas of the palate by irradiation, so that there is a breakdown of normal as well as of neoplastic tissue. If the proper method of treatment is selected in the beginning, many tragic consequences of ill advised radiation therapy may be avoided.

The sensory nerve supply of the hard palate comes entirely from the second division of the fifth cranial nerve; that of the soft palate, from this source and also from the ninth cranial, or glossopharyngeal, nerve. Neurolysis of the second division by injection of alcohol should be an effective means for the relief of pain from lesions of the hard palate, but at the Memorial Hospital this procedure has proved disappointing in comparison with neurolysis of the third division. It has been the experience in that institution that the second division is more difficult to locate by the exploring needle and that even though anesthesia is obtained, the pain is likely to persist. In treating painful lesions of the soft palate I have in several instances exposed and sectioned the ninth cranial nerve in the neck. This procedure has also proved disappointing, mainly because painful lesions of the soft palate almost always extend into other nerve distributions (fifth, seventh and tenth). The most effective measures for relieving pain from palatal tumors are, first, the avoidance of irradiation of the adenoid tumors, second, the use of the smallest and most efficient portals in the irradiation of epidermoid carcinoma, and, third, the hygienic care of radiation reactions.

When intractable pain occurs, as it almost inevitably does in the later stages of uncontrolled cancer, codeine in doses of $\frac{1}{2}$ grain (0.03 Gm.) with 10 grains (0.65 Gm.) of acetylsalicylic acid should be used as long as this prescription is effective; morphine should be reserved, if possible, until the life expectancy is not over a month or two.

Radionecrosis and Osteomyelitis.—These two complications are usually associated and result from the same cause. In the hard palate the bone is covered by a thin layer of soft tissue or tumor, the destruction of which by cancer-lethal radiation leaves devitalized bone exposed. Once an area of heavily irradiated bone has been exposed, spontaneous healing never occurs until after sequestration. For this reason the surgical removal by cautery and chisel of operable epidermoid carcinoma of the hard palate is often the method of choice. The advisability of surgical removal of adenocarcinoma in all cases has already been stressed. Even though a portion of the bone is removed surgically, the defect in the palate opening into the antrum or nasal cavity is usually smaller

than that which occurs following sequestration of bone after cancer-lethal irradiation. With surgical removal, healing of the edges occurs earlier and is more satisfactory, and the period of convalescence is considerably shortened. When radio-osteomyelitis occurs in the hard palate, it is usually preferable to remove the necrotic bone widely so as to promote more rapid healing and relief of symptoms.

The incidence of radionecrosis in the soft palate is much reduced if the radiation is given efficiently, that is, by using the smallest practicable portal and employing the peroral route whenever possible for at least part of the treatment, with supplementary interstitial irradiation in practically all cases, the seeds being implanted under as sterile conditions as can be obtained in this infected area. Radionecrosis in the soft palate is best treated by exercising scrupulous hygienic care, gently removing the slough by traction and clipping with scissors, spraying the base of the wound with a solution of sodium hypochlorite and frequently (every two or three hours) giving irrigations of an alkaline saline solution. As in all necrotic wounds of the oral cavity, there is gross anaerobic saprophytic infection, and the application of an oxygenic preparation, such as zinc peroxide (as developed by Meleney²⁵), is always beneficial. In 32 patients of the present series (28 per cent of those treated by irradiation) there was some degree of radionecrosis and/or radio-osteomyelitis. In most cases these complications followed heavy interstitial dosage. If not too extensive in the palate, radionecrosis is not of serious consequence and seldom leads to fatal complications. Five of these patients remained alive and well for over five years.

Hemorrhage.—One of the occasional concomitants of radionecrosis in the palate is hemorrhage. The palate (hard and soft) does not contain arterial branches large enough to cause serious hemorrhage by erosion within the palate itself. When the radionecrosis or erosion by tumor extends into neighboring structures (lateral pharyngeal wall, tonsillar region), serious bleeding may occur from the erosion of larger vessels. In most of these areas immediate control of the hemorrhage can be effected by tamponage with a gauze pack held by the finger or forceps. Ligation of the external carotid artery on the affected side should be performed immediately. This vessel is best exposed by an incision along the upper anterior border of the sternomastoid muscle, which with the internal jugular vein is retracted posteriorly; by blunt dissection the bifurcation of the common carotid artery is exposed, and the external carotid artery is tied with a fine steel wire ligature. Any form of catgut ligature applied to the external carotid artery will be absorbed and the vessel recanalized within a few days or weeks. In the present series there was hemorrhage in 11 cases (11 per cent of the series). In 5 of these ligations were

25. Meleney, F. L.: *Treatment of Traumatic Wounds with Zinc Peroxide*, New York State J. Med. **39**:2188, 1939.

performed. There was only one immediate fatality from hemorrhage, but all these patients eventually succumbed to extensive disease. The occurrence of hemorrhage therefore indicates that the growth is far advanced and the prognosis poor.

Palatal Defects and Prostheses.—After removal of tumors of the hard palate by cauterization and chisel or after radio-osteomyelitis and sequestration or removal of devitalized bone, defects of the palate opening into the antrum and/or the nasal cavity are common. These defects are similar in nature to those which occur less frequently with cancer of the gum. They produce marked functional disabilities, both in speech and in eating and drinking.

Most of these disabilities can be completely relieved with only moderate difficulty by the construction and use of prostheses (fig. 6D). If a few sound teeth can be preserved in the upper jaw, such devices can be held firmly in place. When such a defect occurs in an edentulous upper jaw, the retention of the appliance constitutes a more difficult mechanical problem but one which can usually be solved by a dentist experienced in the construction of such devices. Dr. Andrew Ackerman, attending dental surgeon at the Memorial Hospital, has published a detailed description of the construction of such prostheses.²⁶

Defects in the soft palate are difficult to repair, an additional reason why epidermoid carcinoma requiring the removal of the entire soft palate should be treated by irradiation rather than by surgical excision. In the removal of an adenocarcinoma or a mixed tumor of the soft palate an effort should be made not to perforate the mucous membrane on the upper surface of the palate; and when the growth occurs near the free edge the line of dissection should be as close to the tumor as safety will permit, in order to avoid a loss in continuity of the structure.

In radionecrosis or deep sepsis of the soft palate, the action of the complicated system of the intrinsic musculature is interfered with; as a result the mobility of the structure is reduced or completely lost, so that deglutition is difficult and speech is altered. In some cases the healing and scarring following the removal of a large tumor produce a retraction of the free edge of the soft palate, resulting in some change in the speaking voice and in some difficulty in swallowing liquids, which tend to enter the nasal cavity. When a defect of the hard palate also involves to even a slight extent the soft palate, the construction of a prosthesis is difficult, since the leakage of fluids into the nasal cavity tends to occur at the posterior margin of the defect, where the movable edge of the soft palate will not remain in close approximation to the device. When a large portion of the soft palate is lost, Ackerman has

26. Ackerman, A. J.: The Dental Care Before, During and After Treatment for Intraoral Cancer, Arch. Clin. Oral Path. 3:141, 1939.

in some cases obtained marked relief from difficulties in speech and deglutition by the use of a device which partly plugs the opening between the oral and nasal pharynxes. In 3 cases in which a mixed tumor of the hard palate was surgically removed, the patient obtained complete relief from the attendant disability by wearing such a prosthesis.

END RESULTS AND PROGNOSIS

The cure rate in the present series of 93 cases of malignant tumor of the palate is given in table 3. Fourteen patients were lost track of or died of other causes after at least a year's freedom from disease, and their cases may be properly considered indeterminate. Of the 79

TABLE 3—*Five Year End Results of Treatment of Cancer of the Palate at the Memorial Hospital from 1929 to 1936, Inclusive*

This series consists of all patients with histologically proved cancer of the palate, both early and advanced, admitted during the specified period. Only those are excluded who, for any reason, were unable to return for treatment, palliation and observation in the outpatient department and those who were lost track of within the first month after no more than one or two visits, "clinic choppers."

Total number of patients	93
Indeterminate group	
Dead as a result of other causes, without recurrence	13
Lost track of, without recurrence	1
Total number of indeterminate results	14
Determinate group (total number minus those of indeterminate group)	79
Failures	
Dead as a result of cancer	55
Lost track of with disease (probably dead)	4
Living with recurrence ..	2
Total number of failures in treatment	61
Successful results (free from disease after five years or more)	18
Net rate of five year cures: successful results divided by number of determinate results (18/79)	23%

patients whose cases are classified as determinate, all observed at least five years, 18 are alive without recurrence, giving a net five year cure rate of 23 per cent.

The prognosis for cure of tumors of the palate is influenced by a number of factors, of which the principal ones are given in table 4. The most significant single prognostic factor is the histologic variety of the growth, as is shown by the respective cure rates for epidermoid carcinoma (19 per cent) and adenocarcinoma (40 per cent). In 8 cases of mixed tumor of the palate not included in table 4, the cure rate was 100 per cent. It is obvious from this table that the variations in prognosis for the minor groups—selected by age, sex and various other factors—are determined largely by the difference in the relative incidence of adenocarcinoma and of epidermoid carcinoma. Since the number of cases of each of these two types of malignant tumor of the palate is not large, the two groups have been combined for some of the prognostic

calculations. Since all the patients with mixed tumors survived, this group is not included in the calculations of the prognosis.

Little discussion can be found in the literature regarding the prognosis of palatal tumors except in Ahlbom's⁵ monograph. He reported permanent cures (five years or more) of 25 per cent of all malignant tumors of the mucous and salivary glands (including the

TABLE 4.—*Factors Influencing the Five Year Cure Rate for Cancer of the Palate in Seventy-Nine Patients with Determinate Results, Observed at the Memorial Hospital from 1929 to 1936, Inclusive*

	Total No. of Patients	No. of Five Year Cures	Percentage of Five Year Cures
Age in years:			
Below 40	4	1	25
40 to 49	11	4	36
50 to 59	21	6	29
60 and over	43	7	16
Sex:			
Male	64	12	19
Female	15	6	40
Size of primary lesion:			
Under 1 cm.....	2	1	50
1 to 1.9 cm.....	7	4	57
2 to 2.9 cm.....	7	4	57
3 to 3.9 cm.....	17	5	29
4 to 4.9 cm.....	15	2	13
5 cm. and over.....	15	1	7
Not stated or scar present.....	16	1	6
Position of lesion:			
Hard palate	23	8	35
Soft palate	50	10	20
Junction between hard and soft palate.	6	0	0
Metastases:			
None on admission.....	42	17	40
None at any time.....	30	15	50
Cervical involvement on admission.....	36	1	3
Cervical involvement after admission...	10	2	20
Systemic involvement after admission..	3	0	0
Sometime during course.....	49	3	6
Histopathologic structure:			
Adenocarcinoma	15	6	40
Squamous carcinoma grade I....	12	7	60
Squamous carcinoma grade II....	36	4	11
Squamous carcinoma grade III.....	7	1	14
Squamous carcinoma ungraded.....	2	0	0
Transitional cell carcinoma grade II...	4	0	0
Transitional cell carcinoma grade III	1	0	0
Melanoma	1	0	0
Rhabdomyosarcoma	1	0	0

parotid and submaxillary salivary glands). That figure cannot be compared directly with those given in this report, since the groups are not of similar composition. Ahlbom emphasized the fact that the prognosis of malignant salivary gland tumors is not as hopeless as many have believed. He also stated that the malignant tumors of salivary gland origin in the palate have a worse prognosis than these tumors in other regions, an observation which is in agreement with the findings at Memorial Hospital.

Age.—The number of malignant palatal tumors in patients under the age of 40 is too small to allow definite conclusions. The cure rates for patients in the fifth and sixth decades, averaging over 30 per cent, are in marked contrast to the 16 per cent cure rate for patients over the age of 60. The better prognosis in the younger age groups undoubtedly is due to the greater incidence of the more curable adenocarcinomas in the younger age group; in the group over the age of 60 there is a preponderance of the more malignant epidermoid carcinoma, and the mortality among these older patients from complications of treatment is higher. Such a trend, from the same cause, is apparent with all forms of intraoral cancer.

Sex.—As with most forms of intraoral cancer, the prognosis of cancer of the palate is better in females (40 per cent cure rate) than in males (19 per cent). Part of this trend may be due to the fact that cancer in the female is more radiosensitive than cancer in the male. However, this would operate only with regard to the epidermoid carcinomas which were treated by irradiation. It may be significant that when the figures are broken down further, of the 15 patients with adenocarcinoma, only 2 of the 7 males survived five years (28 per cent), as opposed to 4 of the 8 females (50 per cent); this suggests that the better prognosis of cancer in females is related not to radiosensitivity alone but also to other sex differences.

Metastases.—As with all forms of cancer, the capacity to metastasize is the predominating factor in the malignancy of palatal tumors. In other words, no matter what the clinical behavior of the primary tumor, its capacity to destroy life is not great until it has metastasized.

When metastases were present on admission, the cure rate of the malignant tumors was only 6 per cent, a figure approximately the same as the cure rate of cancer of the tongue with metastases (8 per cent). The low cure rate in patients admitted with metastases is determined mainly by the significant fact that this group includes the patients admitted in the advanced stages of the disease, practically all of whom have metastases. In the present series the patients with palatal cancers in whom metastases developed after admission had a cure rate of 8 per cent, which is only slightly better than the cure rate of all patients with metastases (6 per cent).

In those patients in whom metastases do not occur at any time during the course of the disease, the chance of cure is 50 per cent (eight times that in patients with metastases). In 18 patients with bilateral metastases there was 1 cure (5 per cent).

Size of the Primary Lesion.—As might be expected, the cure rate of malignant tumors of the palate is considerably influenced by the size of the primary lesion, decreasing from 55 per cent for lesions up to 2 cm. in diameter to 7 per cent for those 5 cm. or more in diameter. This

decrease is caused not only by the greater difficulty in curing the larger lesions but also by the higher proportion of metastases from the larger lesions.

Position of the Lesion.—The difference in the cure rate with respect to the site of the lesion is due mainly to the preponderance of epidermoid carcinoma in the soft palate (77 per cent of the malignant tumors in this area) as compared with the hard palate (23 per cent), where there is a greater proportion of the less malignant adenocarcinoma (57 per cent). Other reasons for the greater comparative malignancy of growths in the soft palate may be that anaplastic epidermoid carcinoma is more apt to occur in this structure adjacent to the nasopharynx and that metastasis is favored by the mobility of the soft palate.

Histopathology.—As previously mentioned, the histologic form of the growth is one of the most significant factors in prognosis. The cure rate of adenocarcinoma (40 per cent) is twice that of epidermoid carcinoma (19 per cent). It is well known that all adenocarcinoma of the oral cavity and, as a matter of fact, any form of adenocarcinoma may recur at long intervals (ten, fifteen or twenty years after apparent control) and that such recurrence is not nearly so frequent with epidermoid carcinoma. Although at the Memorial Hospital it is conceded that with adenocarcinoma the follow-up period of five years is sometimes insufficient, still in order to obtain a reasonable basis for calculation we have used a five year period of control for the whole group. Watson² called attention to the fact that in 4 cases of adenocarcinoma of the oral cavity there was recurrence after ten years. In some cases of apparent late recurrence the possibility of multiple primary lesions of adenocarcinoma must always be considered.

Epidermoid carcinoma of the palate tends to follow the same clinical course as tumors in adjacent sites—palatine tonsil, base of tongue, extrinsic larynx—that is, rapid growth and early metastasis. Adenocarcinoma of either the hard or the soft palate tends to progress slowly in a manner resembling that of the benign mixed tumors, the main difference being that adenocarcinoma metastasizes and mixed tumors do not. The influence of tumor grading is also shown under this heading, but the number of cases is too small to permit any definite conclusions. As might be expected, the cure rate is 100 per cent for the benign mixed tumors.

SUMMARY

Tumors of the palate, both malignant and benign, are discussed from the standpoint of etiology, clinical course and treatment, and details of treatment are discussed.

The net five year cure rate in 93 cases of cancer of the palate was 23 per cent.

MALIGNANT LESIONS OF THE STOMACH

WALTMAN WALTERS, M.D., Sc.D.

ROCHESTER, MINN.

The most frequent site of cancer in the gastrointestinal tract is the stomach, and, as encountered at the Mayo Clinic, this type of cancer affects males three and a half times as frequently as it affects females. The treatment of cancer of the stomach since Billroth first removed the lesion successfully by gastric resection in 1881 has been removal by surgical methods. Although the results of treatment of localized cancer of the stomach of low grade malignancy have been as satisfactory as those of treatment of cancer of the colon, the greater frequency of highly malignant lesions in the stomach and the large number of cases in which the disease does not produce symptoms indicative of gastric neoplasm until late in the course of the disease explain the larger percentage of inoperable malignant lesions of the stomach as compared with inoperable malignant lesions of the colon. The hopeful aspect of the surgical treatment of cancer of the stomach has been that in 28.9 per cent (31.9 per cent, when the figure is adjusted for the normal death rate) of cases in which the lesions were removed surgically, irrespective of the grade of malignancy or involvement of the regional lymph nodes, the patients were living and well five years or more after operation. If the survival curve is compared with the survival curve for the normal population, it is noted that the two curves are practically parallel for the period of more than five years beyond the survival of patients subjected to gastric resection. One of the most hopeful aspects of the study of patients at the Mayo Clinic has been the fact that in cases in which there was no extension of carcinoma or involvement of the lymph nodes, 45 per cent of the patients lived five years or more after leaving the hospital.

Computed on the basis of Broders' index of malignancy, which is dependent on the proportionate number of malignant and normal cells in any typical microscopic field, the five year survival rate after resection was 86.2 per cent in cases in which the lesion was graded 1 (the differentiation ranging from 75 to 100 per cent), 58.8 per cent in cases in which the lesions were graded 2 (the differentiation ranging from 50 to 75 per cent), 30.2 per cent in cases in which the lesions were

From the Division of Surgery, the Mayo Clinic.

The first Walter E. Hering lecture, delivered at the Hahnemann Medical College and Hospital of Philadelphia, Nov. 18, 1941.

graded 3 (the differentiation ranging from 25 to 50 per cent) and 23.3 per cent in cases in which the lesions were graded 4 (the differentiation ranging from 0 to 25 per cent).

AGE AND SEX AS FACTORS IN SURVIVAL AND RESECTABILITY

The youngest patient (including both sexes) on whom partial gastrectomy was performed was 18 years of age. The oldest man was 88 years old, and the oldest woman was 81 years old. It is commonly believed that malignant lesions occurring among younger patients are of a more fulminating character than those which afflict older persons and that the results of treatment of carcinoma among younger patients are therefore considerably poorer than the results obtained with patients of the older age groups. Results of studies of patients at the Mayo Clinic, however, make possible a much more optimistic view, for after surgical removal of malignant lesions of the stomach among patients less than 40 years of age, the five year survival rate was 25.1 per cent (26.0 per cent, when adjusted for the normal death rate) in contrast to the survival rate of 29.7 per cent for patients who were 40 to 49 years of age (31.2 per cent, when adjusted for the normal death rate). The five year survival rate for patients 50 to 59 years of age was 29.2 per cent (32.2 per cent, when adjusted for the normal death rate); the rate for patients 60 to 69 years of age was 28.9 per cent (35.8 per cent, when adjusted for the normal death rate), and that for patients 70 years or older was 29.8 per cent (49.3 per cent, when adjusted for the normal death rate). On the basis of these figures it can be seen that for patients less than 40 years of age who have removable malignant lesions of the stomach, the five year survival rate, although it is somewhat less than that for patients in the older groups, nearly approximates it.

This, I believe, is important, especially since a study of the ratio of gastric resection to the total number of cases of gastric carcinoma in age groups by decades shows that the total percentile average (for the whole series) was 25.5, as compared with a percentile average of 26.7 for patients less than 30 years old, 27.7 in the age group of 30 to 39 years, 25.4 in the age group of 40 to 49 years; 27.4 in the age group of 50 to 59 years, 24.4 in the age group of 60 to 69 years and 20.0 in the age group of more than 70 years.

The rate of resectability among patients less than 30 years of age was 38.7 per cent; among patients 30 to 39 years, it was 41.9 per cent; among patients 40 to 49 years, it was 43.4 per cent, and among patients 50 to 59 years, it was 45.3 per cent. The average rate of resectability for patients in all age groups was 44.4 per cent.

It must be remembered, however, that a relatively small proportion of patients (90) were less than 30 years of age; but 660 patients were

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WALTMAN WALTERS, M.D., Sc.D.

ROCHESTER, MINN.

The most frequent site of cancer in the gastrointestinal tract is the stomach, and, as encountered at the Mayo Clinic, this type of cancer affects males three and a half times as frequently as it affects females. The treatment of cancer of the stomach since Billroth first removed the lesion successfully by gastric resection in 1881 has been removal by surgical methods. Although the results of treatment of localized cancer of the stomach of low grade malignancy have been as satisfactory as those of treatment of cancer of the colon, the greater frequency of highly malignant lesions in the stomach and the large number of cases in which the disease does not produce symptoms indicative of gastric neoplasm until late in the course of the disease explain the larger percentage of inoperable malignant lesions of the stomach as compared with inoperable malignant lesions of the colon. The hopeful aspect of the surgical treatment of cancer of the stomach has been that in 28.9 per cent (31.9 per cent, when the figure is adjusted for the normal death rate) of cases in which the lesions were removed surgically, irrespective of the grade of malignancy or involvement of the regional lymph nodes, the patients were living and well five years or more after operation. If the survival curve is compared with the survival curve for the normal population, it is noted that the two curves are practically parallel for the period of more than five years beyond the survival of patients subjected to gastric resection. One of the most hopeful aspects of the study of patients at the Mayo Clinic has been the fact that in cases in which there was no extension of carcinoma or involvement of the lymph nodes, 45 per cent of the patients lived five years or more after leaving the hospital.

Computed on the basis of Broders' index of malignancy, which is dependent on the proportionate number of malignant and normal cells in any typical microscopic field, the five year survival rate after resection was 86.2 per cent in cases in which the lesion was graded 1 (the differentiation ranging from 75 to 100 per cent), 58.8 per cent in cases in which the lesions were graded 2 (the differentiation ranging from 50 to 75 per cent), 30.2 per cent in cases in which the lesions were

From the Division of Surgery, the Mayo Clinic.

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graded 3 (the differentiation ranging from 25 to 50 per cent) and 23.3 per cent in cases in which the lesions were graded 4 (the differentiation ranging from 0 to 25 per cent).

AGE AND SEX AS FACTORS IN SURVIVAL AND RESECTABILITY

The youngest patient (including both sexes) on whom partial gastrectomy was performed was 18 years of age. The oldest man was 88 years old, and the oldest woman was 81 years old. It is commonly believed that malignant lesions occurring among younger patients are of a more fulminating character than those which afflict older persons and that the results of treatment of carcinoma among younger patients are therefore considerably poorer than the results obtained with patients of the older age groups. Results of studies of patients at the Mayo Clinic, however, make possible a much more optimistic view, for after surgical removal of malignant lesions of the stomach among patients less than 40 years of age, the five year survival rate was 25.1 per cent (26.0 per cent, when adjusted for the normal death rate) in contrast to the survival rate of 29.7 per cent for patients who were 40 to 49 years of age (31.2 per cent, when adjusted for the normal death rate). The five year survival rate for patients 50 to 59 years of age was 29.2 per cent (32.2 per cent, when adjusted for the normal death rate); the rate for patients 60 to 69 years of age was 28.9 per cent (35.8 per cent, when adjusted for the normal death rate), and that for patients 70 years or older was 29.8 per cent (49.3 per cent, when adjusted for the normal death rate). On the basis of these figures it can be seen that for patients less than 40 years of age who have removable malignant lesions of the stomach, the five year survival rate, although it is somewhat less than that for patients in the older groups, nearly approximates it.

This, I believe, is important, especially since a study of the ratio of gastric resection to the total number of cases of gastric carcinoma in age groups by decades shows that the total percentile average (for the whole series) was 25.5, as compared with a percentile average of 26.7 for patients less than 30 years old, 27.7 in the age group of 30 to 39 years, 25.4 in the age group of 40 to 49 years; 27.4 in the age group of 50 to 59 years, 24.4 in the age group of 60 to 69 years and 20.0 in the age group of more than 70 years.

The rate of resectability among patients less than 30 years of age was 38.7 per cent; among patients 30 to 39 years, it was 41.9 per cent; among patients 40 to 49 years, it was 43.4 per cent, and among patients 50 to 59 years, it was 45.3 per cent. The average rate of resectability for patients in all age groups was 44.4 per cent.

It must be remembered, however, that a relatively small proportion of patients (90) were less than 30 years of age; but 660 patients were

between 30 and 39 years of age; 2,217 were between 40 and 49 years of age; 3,622 were between 50 and 59 years of age; 3,404 were between 60 and 69 years, and 897 were more than 70 years of age.

I should like to call attention to the fact that both the surgical rate and the rate of resectability were higher among females than among males and that the hospital mortality rate was considerably lower among females, being 12.8 per cent for gastric resection as compared to 17.3 per cent for gastric resection in males. The five year survival rate, on the other hand, apparently was the same for both males and females, and this was true regardless of the type of surgical procedure that was performed.

FIVE CRITERIA OF LIVINGSTON AND PACK

Livingston and Pack,¹ in their most interesting presentation of published data on the surgical treatment of cancer of the stomach, suggested that "for a study of end results the subject of gastric cancer as a whole must be broken down into several definite subgroups, each of which has a technical significance of its own and an importance which is lost to view unless the particular subgroup is unmistakably identified." These groups include: (1) the total number of patients observed in any given series of cases; (2) the total number of patients who come to operation; (3) the number who undergo resection or gastrectomy; (4) the number who survive resection (immediate survivors) or the number who undergo resection minus the number of those who succumb after resection; (5) the long term survivors, or those still living at a fixed end period, who constitute what might be considered a group definitely cured.

Following this suggestion, my colleagues, Dr. H. K. Gray and J. T. Priestley and I,² with the assistance of Dr. Everett Lewis (assistant in surgery), extracted data from the records of all patients with malignant lesions of the stomach who were seen at the Mayo Clinic during the years 1907 to 1938, inclusive. Follow-up data were obtained concerning 98 per cent of the patients living. In this period 11,000³ patients who had malignant lesions of the stomach were examined at the clinic. Of the 11,000 patients with a malignant process of the stomach, 6,352 underwent operations; 2,840 were subjected to resection. The average mortality rate for partial gastrectomy was 16 per cent.

1. Livingston, E. M., and Pack, G. T.: *End Results in the Treatment of Gastric Cancer: An Analytical Study and Statistical Survey of Sixty Years of Surgical Treatment*, New York, Paul B. Hoeber, Inc., 1939.

2. Walters, W.; Gray, H. K., and Priestley, J. T.: *Malignant Lesions of the Stomach: Results of Treatment in the Years 1907 to 1938, Inclusive*, Tr. West. S. A. **50**:200-218, 1940; *Malignant Lesions of the Stomach: Importance of Early Treatment and End-Results*, J. A. M. A. **117**:1675-1681 (Nov. 15) 1941.

3. Of these, 10,890 had carcinoma, and 110 had sarcoma.

INCIDENCE OF SARCOMA

It might be of interest to call attention to the fact that in the series of patients (6,352) who had malignant lesions of the stomach and who were operated on, 110, or 1.7 per cent, had sarcoma. The most interesting statistical difference between sarcoma and carcinoma is apparent in the distribution in age. Of the patients who had sarcoma, 24.5 per cent were less than 40 years of age, whereas only 6.9 per cent of those who had carcinoma of the stomach were less than 40 years of age. Survival rates accompanying gastric resection for sarcoma closely paralleled those accompanying gastric resection for carcinoma.

POSSIBLE IMPROVEMENT OF RESULTS

In studying the points which have been mentioned thus far, we were interested not only in determining the results of treatment but also in endeavoring to learn whether it would be possible to improve the results of treatment, first, by earlier recognition of the malignant gastric neoplasm before extension occurred and, second, by determining whether preexisting lesions thought to be benign had preceded the development of the malignant lesion.

Indefinite Type of Dyspepsia.—One of the difficulties encountered in early recognition of the symptoms of cancer was the frequency with which an indefinite type of dyspepsia was associated with the lesion until such a time as obstruction or hemorrhage occurred. This indefinite type of dyspepsia was secondary to a disturbance of motility, characterized for the most part by a sensation of fulness or distress after eating, usually associated with loss of weight. However, obstruction as a first symptom of gastric carcinoma was present in 52 per cent of the cases. Bleeding occurred as the first symptom in only 1.3 per cent of the cases of gastric carcinoma. These percentages refer to patients who underwent an operation of any kind and include resection as well as other procedures.

Ulcerlike Symptoms.—The most likely source of diagnostic error was encountered among those patients who had symptoms which are commonly associated with benign ulcer of the stomach and the duodenum. Surprisingly enough, a third of the patients had such a history. In approximately the same proportion (a third) of the patients, the ulcerous type of symptom was the first.⁴ Of even greater importance was the fact that when patients who had this so-called ulcerous type of history followed a medical regimen for ulcer, 80.6 per cent achieved a temporary effective response with relief of pain—suggesting, therefore,

4. Characterized by a burning or gnawing pain in the epigastrium occurring two to three hours after eating which is relieved by food and sodium bicarbonate and by emptying the stomach.

benign ulceration. Several years ago, I said it was my impression that approximately 20 per cent of the patients operated on for cancer of the stomach had received treatment for suspected benign ulcer before a roentgenogram was made which revealed the gastric lesion to be malignant. The corollary of this, it seems to me, is that no matter how typically a patient's history simulates that of a patient who has benign ulcer, the lesion should not be assumed to be benign until it is demonstrated roentgenographically to be situated in the duodenum.

In a recent group of cases reported before the Society of Clinical Surgery in 1941, Stout⁵ called attention to a type of gastric carcinoma which he said appears to be encountered with increasing frequency in resection of the stomach as performed at the Presbyterian Hospital and Sloane Hospital for Women in New York. The carcinoma is of the infiltrating type, involving the mucous membrane and the submucosa of the stomach, and frequently has an origin in gastric ulcer. Many of these lesions were situated along the lesser curvature of the stomach and escaped attention by the roentgenologist because of spasm of the pylorus which produced pyloric obstruction. I, too, have seen lesions of this type, and in many instances the patients have had a long history of so-called ulcer dyspepsia, a history which sometimes covers a period as long as eight years. In such cases, because of the pyloric obstruction present, the diagnosis has been duodenal ulcer.

Since attention has been called to the important part played by gastric ulcer in the treatment of cancer and to the possible error of diagnosing a cancerous gastric ulcer as a benign lesion, it may well be asked, "Why have not all chronic gastric ulcers been operated on?" Experience has shown that many gastric ulcers, usually those of small size and of short duration, may heal if a properly carried out medical regimen in the hospital is instituted; in a few cases large chronic ulcers may heal, at least seemingly so, only to recur later. In my experience many such ulcers, when they have been operated on later, have proved to be malignant. The argument is sometimes advanced that the risk of removal of chronic gastric ulcer is greater than the possibility of the ulcer being malignant or of its becoming malignant. With this I take sharp issue, for the risk associated with removal of gastric ulcer should not exceed a maximum of 5 per cent, and it is possible to operate on a large series of patients who have gastric ulcer and achieve a mortality rate of considerably less than 5 per cent. In point of fact, partial gastrectomy was performed at the Mayo Clinic in 89 cases in 1939, with a mortality rate of 2.2 per cent. This particular series (89 cases) constituted 56 per cent of all patients having gastric ulcer examined at the clinic. In 1940,⁶ partial gastrectomy

5. Stout, A. P.: Unpublished data.

6. Gray, H. K.; Walters, W., and Priestley, J. T.: Report of Surgery of the Stomach and Duodenum for 1940, Proc. Staff Meet., Mayo Clin. **16**:721-727 (Nov. 12) 1941.

for gastric ulcer was performed in 88 cases, with 1 death. Excision of the ulcer or gastroenterostomy or both performed in 17 cases of gastric ulcer resulted in no deaths. Patients were selected carefully, and partial gastrectomy was performed only when the nature of the lesion and the condition of the patient warranted this procedure. From the standpoint of the possibility of recurrence of ulceration, I have never seen a benign gastric ulcer or a gastrojejunal ulcer return after partial gastrectomy in which half or more of the stomach was removed. On the other hand, recurrence of gastric ulceration does occur after medical treatment, but the difficulty of distinguishing between disappearance of the crater of the ulcer resulting from filling in by granulation tissue as against the extension over the crater by the malignant portion of the lesion when viewed roentgenographically has been commented on by Schindler.⁷ This difficulty has been a serious source of error in the treatment of some of the patients, in that the crater disappeared, as did the pain and the blood in the stools, when the patients followed a medical regimen for ulcer. Hence, the lesion was thought to be benign. When symptoms returned or an ulcerous lesion reappeared in the gastric roentgenogram, surgical treatment was advised. At operation in some cases, the lesion proved to be malignant, and in some cases it was inoperable.

I wish to emphasize, therefore, the fact that seeming disappearance of a gastric ulcerating lesion when it is viewed roentgenographically, with relief of symptoms, is not *always* indicative of benignancy, for the reasons I have stated. Patients who have such a condition should be kept under observation, and examinations should be carried out frequently for a period of two years. Supplementing the roentgen report of disappearance of the gastric lesion, a gastroscopic examination should be carried out to confirm such an impression.

Assistance from the Roentgenologist.—When the lesion is situated in the stomach, a source of error which the roentgenologist has frequently emphasized may arise, namely, a definite percentage of carcinomatous ulcers have the roentgen appearance of benign ulcer. In 10 per cent of the cases in which resection was performed for gastric carcinoma, the lesions were reported by the roentgenologists to be gastric ulcer. In 1939,⁸ of 131 cases in which gastric resection was performed for malig-

7. Schindler, R.: Early Diagnosis of Cancer of the Stomach: Gastroscopy and Gastric Biopsies, Gastrophotography, and X-Rays, *J. Nat. Cancer Inst.* **1**:451-471 (Feb.) 1941.

8. Gray, H. K.: Report on Surgery of the Stomach and Duodenum, 1939: Gastric Ulcer, *Proc. Staff Meet., Mayo Clin.* **15**:710-711 (Nov. 6) 1940. Priestley, J. T.: Report of Surgery of the Stomach and Duodenum, 1939: Duodenal Ulcer, *ibid.* **15**:707-709 (Nov. 6) 1940. Walters, W.: Report on Surgery of the Stomach and Duodenum, 1939: Malignant Lesions of the Stomach, *ibid.* **15**:712-717 (Nov. 6) 1940.

nant lesion of the stomach at the Mayo Clinic, the roentgenologist had reported the gastric lesion to be a gastric ulcer in 9 cases, or 7 per cent. At the clinic, in the period of 1939 and 1940, in 237 cases in which the diagnosis was gastric ulcer and in which the patients underwent operation, 19 of the patients, or 8 per cent, were found to have malignant gastric lesion.

The ability of roentgenologists to recognize the presence of gastric lesions, when they are present, in from 98 to 99 per cent of the cases is a truly great achievement, especially when they are able to recognize lesions which in many instances are no larger than a thumbnail. In the series on which this paper is based, in the cases in which partial gastrectomy was performed for carcinoma (2,772), although the presence of a gastric lesion was demonstrated in 99 per cent of the cases, in only 75.3 per cent was the lesion reported unqualifiedly as being malignant.

Studies of Gastric Acidity.—With the large group of patients having histories suggesting benign ulcer and with the definite possibility that the error of reporting cancerous ulcer as benign ulcer roentgenographically may occur, it seems that studies of gastric acidity may be helpful in arriving at the differential diagnosis. The significance of a gastric lesion associated with achlorhydria (indicating that the lesion is malignant) is well known to all. Yet, only 51.4 per cent of the patients on whom partial gastrectomy was performed had achlorhydria, and achlorhydria was present in practically the identical percentage of those for whom only palliative procedures could be carried out. In other words, 50 per cent of the patients operated on for carcinoma of the stomach had some amount of free hydrochloric acid, and in comparing the values for hydrochloric acid it was noted that in members of both groups, namely, those who underwent resection as well as those for whom palliative procedures were carried out, free hydrochloric acid was present, ranging from 1 to 29 degrees in approximately 30 per cent of the cases; from 30 to 49 degrees in approximately 15 per cent of the cases, and 50 degrees or more in approximately 5 per cent of the cases. To express it differently, approximately 20 per cent of the patients operated on for carcinoma of the stomach had a free hydrochloric acid content (Töpfer's method) of more than 30 degrees. It is apparent, therefore, that the presence of hydrochloric acid in the gastric contents does not exclude the possibility that the gastric lesion is malignant.

Gastroscoy.—The development of gastroscopy in the United States in the past few years has added materially to the recognition and observation of intragastric lesions. The method has been helpful also in decreasing that percentage of roentgenologic error which arises because of the difficulty of visualization and identification of lesions situated high in the posterior wall or the fundic end of the stomach. Gastroscopic

examination should be carried out in every case in which the clinical picture would lead the physician to suspect the possibility of an intra-gastric lesion after an uncertain report has been obtained subsequent to roentgenoscopic and roentgenographic examination of the stomach. The procedure is helpful also in following the course of the patients by direct observation of the gastric ulcer when medical treatment has been instituted as a trial measure.

Medical Treatment.—It is apparent, therefore, that much care must be exercised in the selection of patients for medical treatment when they have been reported as having benign gastric ulcer, in view of the approximate 10 per cent of the cases, previously mentioned, in which patients supposed to have benign lesions were found at operation to have malignant lesions. In statistics from other clinics the incidence of malignant changes in gastric ulcer has been stated to be from 10 to 20 per cent. Sir James Walton⁹ stated that the figures of Stewart¹⁰ are now generally accepted, namely, that 9.5 per cent of chronic gastric ulcers become carcinomatous and that 17 per cent of carcinomas originate in chronic gastric ulcer. Katsch¹¹ reported an incidence of malignant change of 20 per cent, and Finsterer¹² found that in 532 cases in which resection had been performed for gastric ulcer, the ulcer was carcinomatous in 141, an incidence of "20.9 per cent."

THE ROLE OF BENIGN GASTRIC TUMORS, INCLUDING POLYPS

The most frequent benign tumors of the stomach are small fibroadenomas. These vary in size, frequently are small and may produce no symptoms until bleeding occurs. Other benign gastric tumors are leiomyoma, fibromyoma, neurofibroma and adenomyoma.

The symptom most frequently produced by benign tumor of the stomach is bleeding. Several of the patients had no evidences of an intragastric lesion until during the course of the examination designed to rule out such lesions as a source of the anemia which had been noted, the presence of an unsuspected gastric or colonic polyp or polyps was discovered on roentgen examination. Many of the patients had been treated for suspected primary anemia.

Some of the pedunculated gastric polyps prolapse at times through the pylorus, producing various types of obstructive dyspepsia. In some cases the bleeding may occur so gradually that the patient's first symp-

9. Walton, J.: Carcinoma of the Stomach, *Lancet* 1:1101-1107 (May 16) 1936.

10. Stewart, cited by Walton.⁹

11. Katsch, cited by Hurst, A. F.: Carcinoma of the Stomach, *Lancet* 2:1455 (Dec. 18) 1937.

12. Finsterer, H.: Malignant Degeneration of Gastric Ulcer, *Proc. Roy. Soc. Med.* 32:183-196 (Jan.) 1939.

toms are weakness and asthenia due to secondary anemia, and a bleeding gastric lesion is recognized only on roentgen or gastroscopic examination of the stomach.

In my experience, the lesions which produce these symptoms most frequently are leiomyomas, some of which reach a large size. On April 21, 1938, I operated on a woman from whose stomach I removed a hemorrhagic degenerating leiomyoma, 12 by 13 by 9 cm. Her only symptom was weakness, but she had noticed the tumor herself by inspection and palpation of the abdomen.

Conversion into Malignant Tumor.—The tendency of some of these seemingly benign tumors to metastasize is evidenced by the case of Sworn and Cooper.¹³ These observers reported the presence of hepatic metastasis in a patient with leiomyoma of the stomach. It is, of course, possible for such a lesion to degenerate and become malignant leiomyosarcoma. On June 14, 1940, I operated on a woman who had a large degenerating leiomyosarcoma, 7 by 6 by 5 cm. The presence of the tumor had been known for four years. So much bleeding had occurred from it that at one time erythrocytes had numbered 1,900,000, with a corresponding decrease in hemoglobin. The tumor was removed by partial gastric resection. She returned to the clinic for reexamination on March 3, 1941, nine months after operation; at this time her general health was excellent. The value for hemoglobin was 12.1 Gm. per hundred cubic centimeters, and there was no evidence of recurrence.

Miller, Eliason and Wright¹⁴ reported the incidence of malignant degeneration to be 35 per cent in 23 specimens of gastric tumor subjected to careful histologic study. Brunn and Pearl¹⁵ found that in 12 per cent of 82 collected cases malignant degeneration was reported. Rieniets,¹⁶ while he was a fellow in surgery in the Mayo Foundation for Medical Education and Research (1940), made a comprehensive study of gastric adenoma and stated that "the relationship of gastric adenomas to adenocarcinoma is not to be interpreted in the sense that all adenomas become malignant, but the writer's study proves conclusively that these adenomas

13. Sworn, B. R., and Cooper, T. V.: Leiomyoma of the Stomach, *Lancet* 1:428-429 (Feb. 19) 1938.

14. Miller, T. G.; Eliason, E. L., and Wright, V. W. M.: Carcinomatous Degeneration of Polyp of the Stomach: Report of Eight Personal Cases with a Review of Twenty-Four Recorded by Others, *Arch. Int. Med.* 46:841-878 (Nov.) 1930.

15. Brunn, H., and Pearl, F.: Diffuse Gastric Polyposis: Adenopapillomatosis Gastrica; Report of Five Proven and Seven Probable Cases, *Surg., Gynec. & Obst.* 43:559-598 (Nov.) 1926.

16. Rieniets, J. H.: A Comprehensive Study of Gastric Adenomas with Special Reference to Their Pathologic Anatomy, Complications, and Tendency to Malignant Transformation, Thesis, University of Minnesota Graduate School, 1940.

are potentially malignant, and the size and volume of the tumor alone are not the determining factors for malignancy but rather the cellular activity of the neoplastic process."

Indications for Removal.—It seems clear, therefore, that the indications for removal of benign tumor of the stomach are apparent; it should be removed not only because of the symptoms of bleeding and anemia which the tumor itself produces but also because of the possibility that malignant degeneration may take place, especially if the tumor contains adenomatous and myomatous tissue.

PATHOLOGIC NATURE OF THE LESIONS

In a discussion of survival rates, the most important details regarding the pathologic nature of the lesion should of course be known. While the size of the tumor varied, as might be expected, from as small as 1 or 2 cm. to as much as 9 cm. or more, it is interesting to note that the least extensive type of gastric resection, namely, local excision, occasionally was performed for lesions of small size (averaging 3.4 cm. in diameter).¹⁷ In contrast to this were the cases in which the posterior Polya type of operation was performed; in these the average diameter of the lesions was 6.2 cm. The anterior Polya-Balfour operation was performed when the lesions were, on the average, 7 cm. in diameter, while total gastrectomy was employed for lesions 9.2 cm. or larger. It is interesting to note that among the various lesions there is a definite and progressive increase in the proportion of involvement of lymph nodes as the size of the lesion increases but that there is also a definite decrease in the value for hemoglobin as lesions increase in size. The effect of the size of the lesion on the mortality rate accompanying gastric resection is interesting, for the lesions of smaller size (3 cm. or less) were accompanied by a definitely lower mortality rate (averaging about 6 or 7 per cent). As the lesions increased in size (7 cm. or more in diameter), the mortality rate increased.

Metastasis.—In 45.3 per cent of the cases in which resection was done, metastasis was not present, while in 53.5 per cent of such cases metastasis was found in the gastric lymph nodes. Involvement of the retroperitoneal or other abdominal lymph nodes or hepatic metastasis was present in approximately 1 to 2 per cent of the cases in which resection was done. On the other hand, in those cases in which palliative operations were performed extragastric involvement of lymph nodes was present in 12.6 per cent; extragastric involvement of the liver was present in 12.8 per cent, and abdominal metastasis was present in 14.7 per cent.

17. Operations of this type for small gastric lesions, although frequent in the period preceding the advent of partial or subtotal gastrectomy, have in the last twenty-five years been used only rarely.

INDICATIONS FOR OPERATION

In many instances roentgenologists have attempted to aid the clinician and the surgeon further by expressing an opinion as to the operability of the lesion which they see roentgenographically, the operability being based, in their minds, on whether or not there seems to be a sufficient portion of normal stomach above the lesion to permit removal of the lesion with restoration of gastrointestinal continuity. For example, those lesions involving the lower half of the stomach might be considered to be operable as well as certain of those in the middle third part of the stomach. In 20 per cent of the cases in which surgical exploration was undertaken, although the lesion was considered roentgenologically to be inoperable or of doubtful operability, the lesion proved to be removable. With recognition of this error of interpretation in recent years, the percentage of patients who have undergone exploratory operation for cancer of the stomach has increased progressively. The rate of removability likewise has increased because of the willingness of surgeons to remove, if possible, every malignant gastric lesion that has not metastasized to regions from which it cannot be removed. The extent to which this may be carried is evidenced by the fact that although up to 1938, inclusive total gastrectomy had been performed 27 times, during 1937, 1938, 1939 and 1940 total gastrectomy was performed 16 times, with a mortality rate of 31.2 per cent. In 1940, total gastrectomy was performed 8 times, with 1 death. In the last few years, by means of a transthoracic approach, lesions of the lower end of the esophagus and the cardial end of the stomach have been successfully removed; the diaphragm has first been split, and then it has been resutured together around the stomach below the point of esophageal gastric anastomosis. Cases in which this procedure was successful have been reported by Phemister,¹⁸ Ochsner¹⁹ and me.²⁰

I have previously presented some of the statistics concerning favorable results in the surgical extirpation of lesions confined to the stomach and those of a low degree of malignancy. I have also called attention to favorable results of partial gastrectomy for patients in the younger age groups, i. e., between the ages of 20 and 40 years. I should like to

18. Adams, W. E., and Phemister, D. B.: Carcinoma of the Lower Thoracic Esophagus: Report of a Successful Resection and Esophagogastronomy, *J. Thoracic Surg.* **7**:621-632 (Aug.) 1938. Phemister, D. B.: The Operative Treatment of Carcinoma of the Esophagus, *Illinois M. J.* **79**:497-500 (June) 1941.

19. Ochsner, A., and DeBakey, M.: Surgical Aspects of Carcinoma of Esophagus: Review of Literature and Report of Four Cases, *J. Thoracic Surg.* **10**:401-445 (April) 1941.

20. At the time of writing, the first patient for whom this type of operation was utilized by me is in the hospital on the twenty-first postoperative day. In this case the procedure included transthoracic esophageal gastric resection and esophageal gastric anastomosis.

amplify those statements somewhat by stating that, in spite of the fact that the average age at which the patients who had cancer of the stomach were operated on in the present series was 55.5 years, 20 per cent of all patients survived for ten years; 15 per cent survived for fifteen years; 11 per cent survived for twenty years or more, and 6 per cent survived for twenty-five years or more. I wish to emphasize again that when these survival rates are compared with the normal mortality rates in the general population, it is noted that the two curves are practically parallel from the period of five years beyond the survival of the patients who survived resection.

TYPES OF OPERATION

The operation of gastric resection, referred to as partial or subtotal gastrectomy, has been established as a procedure of greatest value in the radical removal of a malignant lesion of the stomach. The reason for this is that the lower limit of extension of gastric carcinoma is the pylorus, and if the duodenum is divided below the pylorus, so that all the lower part of the stomach, including the pylorus and the gastrohepatic and the gastrocolic omentum, is removed, extension of the neoplasm beyond these areas is effectively prevented, unless extension has already occurred, as in the case of involvement of the retroperitoneal lymph vessels. By removal of part of the stomach at as high a level as is consistent above the site of the tumor and the attached omentum containing lymph nodes, the possibility of direct extension of the carcinoma to areas beyond the lesion, as well as through the intragastric lymphatic channels, is obviated.

The operations which have been most effective are those described by Polya and Balfour, which are modifications of the Billroth II operation. In the Polya operation the remaining portion of the stomach is joined to the side of the jejunum, posterior to the colon. Balfour modified the operation by advising that a longer loop of jejunum be used and that the anastomosis be made anterior to the colon. When this is done, it is usually advisable to establish enteroanastomosis between the jejunal loops to prevent gastric retention. In 24 per cent of the cases in which partial gastrectomy was done, the operation was of the anterior Polya-Balfour type, and in 46 per cent it was of the posterior Polya type, the total for both procedures being 1,923 or 2,745 cases in which partial gastric resection was carried out for carcinoma (the figure of 2,745 does not include 27 cases in which total gastrectomy was performed for carcinoma).

Generally speaking, the Polya-Balfour operation was used in those cases in which extensive resection was necessary because of the large size of the lesion.

The Billroth I operation was used only 170 times, but the mortality rate associated with it was the lowest of all such rates for the various procedures, being 11.2 per cent. The lesions for which this operation were performed were next to the smallest in size, and the five year survival rate associated with it was better than the five year survival rate accompanying the Polya type of procedure.

There was a small group of cases in which local excision of the tumor was carried out. The reason for utilization of this procedure has been explained earlier in the paper. In most of these cases, operation was carried out before the advent of the almost routine use of the Polya type of resection. As the results of treatment in these cases are examined, it is interesting to note that the average size of the lesion for which this procedure was carried out was 2.7 cm., or only a half to a third of that for which the Polya type of procedure was carried out. In addition, in approximately 53 per cent of the cases in which local excision was done, the lesions were graded 1 or 2, in contrast to lesions of grade 1 or 2 in only 25 per cent of cases in which the Billroth I operation was performed and lesions of grade 1 or 2 in only 19.4 per cent of cases in which the Polya or Polya-Balfour operation was performed. It may be said, however, that in some cases in which the tumor is small and in which the lesions are of a low degree of malignancy, wide removal of the lesion may be followed by an excellent result and hence might be indicated for elderly or debilitated patients.

Palliative Operations.—For the most part, the radical removal of neoplasms of the stomach has been considered thus far, and I have emphasized throughout this paper the relationship of the survival rate in such cases to the various factors of age, size of the lesion, sex of the patient and type of operation performed. There was, of course, a large number of cases (1,039) in this series in which gastric extension of carcinoma made complete removal of the malignant neoplasm impossible, but in which, for one reason or another (usually obstruction), palliative types of operation, such as gastroenterostomy or jejunostomy, were performed. The mortality rate accompanying palliative operations of this type almost equaled that accompanying gastric resection. A five year survival rate of 1.1 per cent was associated with the palliative operations, in contrast to a rate of 0.6 per cent associated with surgical exploration. This seems to be direct evidence in support of the viewpoint that palliative operations for inoperable, irremovable gastric neoplasm are seldom advisable.

MORTALITY RATE

In the management of complicated malignant lesions of the stomach the mortality rate is directly proportional to the experience of the surgeon and the condition of the patient. It will also depend on the extent to

which the surgeon is willing to remove large portions of the stomach for the purpose of excision of malignant lesions. For example, the risk of total gastrectomy is considerably higher than that of subtotal gastrectomy. Likewise, the operation is more difficult, and there is more possibility of postoperative complications when the lesions are large and are situated in the middle or the upper part of the stomach and have produced a considerable degree of debility as a result of obstruction, bleeding and ulceration. The average mortality rate for the series (1907 to 1938, inclusive) in which partial gastrectomy was done was 16 per cent, but in 1940, the mortality rate was 8.5 per cent in 117 cases in which this operation was carried out for cancer of the stomach.

I think it is worth while to recapitulate, somewhat, what has been said concerning those factors which influence the mortality rate. First of all, it has been shown that the younger the patient, the lesser the risk of partial gastrectomy and that this risk increases progressively with age, the average risk in the series being 16 per cent for all age groups. The mortality rate for gastric resection among females was somewhat less than that for gastric resection among males; it was 12.8 per cent for the females and 17.3 per cent for the males. The risk of resection was proportionate to the size of the lesion, and this was probably due to the fact that the larger the lesion, the greater the extent of stomach it was necessary to remove—hence, the more difficult the operation. Similarly, the grade of malignancy also influenced the risk of gastric resection, for the risk increased progressively as the grade of malignancy increased, being 7.5 per cent in cases of grade 1 tumor and 18.3 per cent in cases of grade 4 tumor.

An additional factor influenced the mortality rate of gastric resection. It is a factor which I have not as yet mentioned and which may have more significance than may appear on superficial examination; it is that the risk of resection among those patients in whom free hydrochloric acid was present was just half that among those who had achlorhydria, being 10 to 12 per cent in cases in which free hydrochloric acid was 30 or more degrees and 20.2 per cent in cases in which achlorhydria was present.

It might be assumed that patients with free hydrochloric acid are those who have smaller lesions which might be of the lower degrees of malignancy, but earlier in this paper I stressed the fact that such is not the case, for the percentage of small and large lesions and the percentage of lesions of low and high grade malignancy among patients with free hydrochloric acid and those with achlorhydria are about comparable.

SUMMARY

The hopeful aspect of the surgical treatment of cancer of the stomach has been that in 28.9 per cent (31.9 per cent, when the figure is adjusted for the normal death rate) of cases in which the lesions were removed

surgically, irrespective of the grade of malignancy or involvement of the regional lymph nodes, the patients were living and well five years or more after operation. If the survival curve is compared with the survival curve for the normal population, it is noted that the two curves are practically parallel for the period of more than five years beyond the survival of patients who have undergone gastric resection.

The five year survival rate after resection, computed on the basis of Broders' index of malignancy, was 86.2 per cent in cases in which the lesion was graded 1 (the differentiation ranging from 75 to 100 per cent) ; 58.8 per cent in cases in which the lesion was graded 2 (the differentiation ranging from 50 to 75 per cent) ; 30.2 per cent in cases in which the lesion was graded 3 (the differentiation ranging from 25 to 50 per cent), and 23.3 per cent in cases in which the lesion was graded 4 (the differentiation ranging from 0 to 25 per cent).

The five year survival rate and the rate of resectability among patients less than 40 years of age were surprisingly high when compared with the general average. In all age groups the rate of resectability was higher, and the operative risk was less in females than in males.

In 1.7 per cent of the cases resection was done for sarcoma.

Attention is called to the high incidence of ulcer-like dyspepsia among patients who have cancer and to the temporary effective response, measured by relief of pain, to a nonsurgical regimen in 80.6 per cent of such cases, indicating the danger in the making of a differential diagnosis between benign and malignant lesions of the stomach on the basis of symptoms alone.

Although the roentgenologist was able to demonstrate the presence of a lesion in the stomach in 98 to 99 per cent of the cases, in only 75.3 per cent was he able to designate the lesion unqualifiedly as cancer. On the other hand, it is interesting to note that a report of gastric ulcer was made by the roentgenologist concerning 10 per cent of the patients.

About 20 per cent of the patients operated on for cancer of the stomach had a free hydrochloric acid content of more than 30 degrees.

Precancerous lesions, such as chronic gastric ulcer and benign polyps, should be removed surgically.

The preferable procedure in the treatment of cancer of the stomach is partial gastrectomy by the method of Billroth; for the most part, I employed this operation as modified by the indirect anastomosis of Polya or Polya-Balfour type. Anastomosis of the Billroth I type was used successfully in a series of cases and was associated with a lower mortality rate than the Polya operation.

SUPERFICIAL SPREADING TYPE OF CARCINOMA OF THE STOMACH

ARTHUR PURDY STOUT, M.D.

NEW YORK

Carcinoma of the stomach starts in the epithelial mucus-producing cells of the mucous membrane and grows outward from one or more focal points in all directions, i. e., into the lumen, along the gastric wall parallel to the lumen and toward the serosa. However, different tumors vary in the speed with which they grow in these various directions, and this accounts for the morphologic characteristics of the different gross types of gastric carcinoma. For instance, there is the fungating tumor, which grows chiefly into the lumen; there is the *linitis plastica* type, the growth of which runs parallel to the lumen in all of the gastric coats, and there are the ulcerated cancer and the cancer developing at the margin of a preexisting peptic ulcer, the growth of which is usually directed chiefly toward the serosa. In a little more than half of the resected stomachs, growth apparently occurred at comparable rates in all three directions, producing a tumor without distinguishing characteristics.

Until March 1937, the foregoing classification covered all the different gross forms of gastric carcinoma which I had observed. In that month I encountered the first of a series of tumors which displayed a different pattern of growth. In this form, growth starts in the mucosa and spreads superficially in the mucosa and the submucosa without penetrating deeply into the muscularis until it has covered a considerable surface area. In 1 instance the area involved measured 9 by 6 cm. without penetration beneath the submucosa. Cases have accumulated rapidly until now I have a collection of 15 cases of tumor of this type. In all of them the antral portion of the stomach in the vicinity of the lesser curvature was involved.

Grossly, carcinoma of this type is characterized by reddening, irregularity and slight nodular thickening of the diseased mucosa. Almost always this is associated either with a shallow bowl-shaped ulcer extending to the submucosa or with a characteristic deep-penetrating peptic

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From the Surgical Pathology Laboratory of the Columbia University College of Physicians and Surgeons and the Department of Surgery of the Presbyterian Hospital.

ulcer, from the periphery of which the superficial tumor growth spreads outward in the mucosa and the submucosa. In 9 of the cases the growth started at the margin of a peptic ulcer; in 5 the cancer was ulcerated, and in 1 case there was only superficial erosion without real ulceration. Despite the fact that the tumors were superficial, it was observed, when resection was performed, that 7 of the 15 had already metastasized either to the superior or to the inferior gastric lymph nodes

The histologic appearance of neoplasms of this type varies greatly in degree of differentiation, from the formation of atypical acini and more



Fig 1 (case 5) —Superficial spreading carcinoma with erosion but no true ulceration. The stomach is shown opened along the greater curvature with the hypertrophied pylorus at the left. The tumor covered an area 6 by 9 cm. on the lesser curvature and the adjacent anterior and posterior walls of the distal half of the stomach. There was patchy involvement of the mucosa and submucosa alone.

or less mucin to completely undifferentiated carcinoma with rounded cells appearing singly or in small clusters. Four of the cancers in this series involved the mucosa in a patchy fashion with areas free from neoplasm between the islands. However, the important feature common to all, whether they started from a single focus or from multiple foci, was the superficial spread. In only 5 of the 15 cases was there any invasion of the muscularis, and in these the penetrating growth was

found in only one microscopic area after examination of numerous preparations. In the majority of the cases the cancerous growth was associated with fibrous thickening of the gastric wall and hypertrophy of the muscular coat. The pyloric ring muscle was hypertrophied in 10 of the 15 cases. In all, gastritis involved the mucosa and usually the other coats as well.

The clinical problem of diagnosis was to decide whether the patient was suffering from gastritis, peptic ulcer, cancer or some combination



Fig. 2 (case 14).—Superficial ulcerated carcinoma with spread into the surrounding mucosa, covering a total area 3.2 by 3 cm. The stomach has been opened along the greater curvature with the hypertrophied pylorus at the left. The cancer involves the lesser curvature and the adjacent anterior and posterior walls near the pylorus.

of these three. Most of the patients had suffered from one to ten years with symptoms suggesting gastric or duodenal ulcer. Two thirds of them actually had peptic stomach ulcers with hypertrophy of the pyloric and antral muscles, and 14 were noted to have more or less six hour retention, probably due to muscular spasm since in none of them was

the stomach mechanically obstructed. Acid secretion was variable. Most of them had sufficient fibrosis to stiffen the gastric wall. This, together with the extension of the cancer in the mucosa, muscularis mucosae and submucosa, caused distortion of the peristaltic waves and disarrangement of the mucosal folds, sometimes with the formation of small mucosal nodules which could be visualized by roentgenograms and seen through a gastroscope.

From March 1937 to Oct. 12, 1941, 69 gastric neoplasms diagnosed as carcinomas have been resected in the Presbyterian Hospital. As 15



Fig. 3 (case 14).—At the left is seen the bed of the shallow ulcer shown in figure 2. The carcinoma occupying it extends through the still undestroyed mucosa to the right. It has just penetrated the muscularis mucosae and has invaded lymphatics in the superficial submucosa. Metastases were found in the superior gastric lymph nodes, but there was no deeper penetration of the wall than is shown.

of them showed the superficial spreading type of growth, this means that nearly 22 per cent were of a type never before seen among the 105 cases of carcinoma in which resection was done from 1916 through February 1937. This form of cancer of the stomach is not unknown, but its existence is appreciated by few of those concerned with diagnosis.

Cases have been reported by Mallory,¹ Ewing,² Konjetzny,³ Gutmann, Bertrand and Péristiany⁴ and Baker,⁵ and suggested by Schindler and associates⁶ but without exact description. Ewing and Mallory both expressed the belief that a majority of these cases, especially those in which the involvement is limited to the superficial part of the mucosa and in which skip areas are present, leaving free zones between, are instances of so-called cancer in situ, meaning by that carcinoma developing simultaneously in multiple foci. This hypothesis seems to me to

TABLE 1.—Data on Fifteen Patients with Superficial Spreading Carcinoma of the Stomach

Patient	Sex	Age, Years	Duration of Symptoms Before Operation, Mo	Pyloric Hypertrophy	Six Hour Retention, per Cent	Acidity *		Associated Classification †	Isolated Superficial Foci	Invasion of Muscularis	Metastasis to Lymph Nodes	Time After Operation, Mo	Result
1	F	66	12	Yes	9			U C	Yes	No	Yes	13	Died
2	M	45	84	Yes	90	38/51	98/111	C P U	No	Yes	No	47	Well
3	M	51	36	No	50			C P U	Yes	No	No	36	Well
4	M	37	8	Yes	15	0/5	10/58	C P U	No	No	Yes	36	Well
5	M	50	12	Yes	50	0/20		None	Yes	No	No	39	Well
6	F	61	8½	No	80			C P U	No	No	No	33	Well
7	M	34	120	Yes	50	...		U C	Yes	No	No	24	Well
8	M	60	5	No	50	28/38		U C	No	Yes	No	31	Well
9	F	54	12	No	95	...		C P U	No	Yes	No	18	Well
10	M	52	4	Yes	5	22/34	65/80	U C ‡	No	No	Yes	17	Well
11	F	55	24	Yes	60	0/89		C P U	No	Yes	Yes	19	Well
12	M	50	60	No	Slight	18/22		C P U	No	No	No	16	Well
13	F	67	12	Yes	30	25/55		C P U	No	No	Yes	10	Well
14	F	58	24	Yes	10	24/43	71/91	U C	No	No	Yes	9	Well
15	M	56	24	Yes	100		0/165	C P U	No	Yes	Yes (Recent)		

* On the left, free hydrochloric acid over total acid; on the right, the same forty minutes after the injection of histamine

† U.C., ulcerated cancer; C.P.U., cancer in a peptic ulcer.

‡ Unrelated peptic ulcer also present.

1. Cabot Case 21111, New England J Med **212**:481, 1935. Mallory, T. B. *ibid.* **225**:87, 1941.

2. Ewing, J.: Neoplastic Diseases, ed. 3, Philadelphia, W. B. Saunders Company, 1928, p. 688; ed. 4, 1940, pp 709-711; Am. J. Surg. **31**:204, 1936.

3. Konjetzny, G. E.: Compt. rend. II^e Cong. internat. de gastro-entérol, 1937, p. 590.

4. Gutmann, R. A.; Bertrand, I., and Péristiany, T. J.: Le cancer de l'estomac au début, Paris, Gaston Doin, 1939, pp. 92, 218 and 389-404.

5. Baker, J. W.: Northwest Med **40**:277, 1941.

6. Schindler, R.; Steiner, P. E.; Smith, W. M., and Dailey, M. E.: Surg., Gynec. & Obst. **73**:30-39, 1941.

require further investigation before it can be accepted, but whether the growth starts from a single focus or from multiple foci, the involvement and spread remain superficial.

It has been natural to speculate as to why I should suddenly begin to note these cases in considerable numbers when they were never noted at all by me before 1937. Since in 14 of the 15 the cancer was associated with an ulcer of either a benign or a malignant type, it was decided to determine the percentage of cases of ulcerated cancer and cancer in peptic ulcer in the total number of cases of carcinoma of the stomach in which resection was done in each succeeding quinquennial period, beginning in 1916. The results are shown in table 2. There has been an almost steady increase in the percentage of cases in which carcinoma starts in, or simulates, peptic ulcer of the stomach. This seems to me to parallel

TABLE 2.—Percentage Relation of Cases of Ulcerated Gastric Carcinoma and Carcinoma in Peptic Ulcer to Total Number of Cases of Carcinoma of the Stomach in Which Resection Was Done at the Presbyterian Hospital

Quinquennial Period	Total Cases in Which Resection Was Done	Cases of Ulcerated Carcinoma and Carcinoma in Ulcer	
		Number	Per Cent
1916-1920.....	17	2	11.7
1921-1925.....	22	4	18.0
1926-1930.....	21	3	14.2
1931-1935.....	45	10	22.2
1936-1940.....	59	22	37.3

the increase of interest in patients with ulcerated lesions of the type described and the marked development of ability to recognize the condition at an earlier stage, so that earlier operations are done. Whether or not this is the sole explanation for the sudden appearance of the superficial spreading type of cancer in resected stomachs is uncertain. Two thirds of the patients suffered from gastric symptoms for more than a year preceding operation, and a like proportion of the cancers covered areas of mucosal surface in excess of 12 sq. cm. with a maximum of 54 sq. cm. Therefore it would seem that plenty of opportunity was afforded for deeper penetration if these tumors had behaved like those diagnosed as gastric carcinoma before 1937.

Whatever the explanation of the sudden appearance of the superficial spreading type of gastric carcinoma may be, the results of treatment by partial gastrectomy have been gratifying, even though not enough time has elapsed to determine the five year survival rate. All of the patients survived the operation; 1 died of cancer thirteen months after

resection. Of the 14 survivors at the time of writing, 4 have passed three years; 3 are living between two and three years; 4, between one and two years; 3, less than one year after operation. All of these survivors are symptom free.

It seems probable that concentration on the diagnosis of early cancer of the stomach, particularly in the group suffering from ulcer symptoms, will bring to light in a larger number this type of superficial spreading carcinoma, which seemingly offers a far better hope of cure by surgery than the average.

PATHOGENESIS OF CHOLECYSTITIS

NATHAN A. WOMACK, M.D.

AND

EUGENE M. BRICKER, M.D.

ST. LOUIS

Considerable confusion exists at the present time as to the pathologic and the physiologic mechanism involved in inflammatory processes in the gallbladder. These difficulties have been reflected in the wide divergence of opinion relative to the treatment of these inflammatory processes in various stages. Efforts directed at the solution of the problem by clinical statistical methods have apparently added more to the confusion than to the clarification of opinion. The following studies are based on an attempt to approach a better understanding of the subject by experimental and clinical analysis of the pathologic factors involved.

Any explanation of the pathogenesis of cholecystitis must take account of many unique features by which cholecystitis differs from most inflammations elsewhere in the body. These features present themselves both clinically and pathologically.

In the clinical picture of cholecystitis there are many characteristics that are unusual when compared with inflammation in other organs. It is one of the inflammatory processes most frequently encountered in the abdomen. Mentzer¹ noted gross evidence of cholecystitis in 62 per cent of the gallbladders removed at necropsy in a study of 612 patients. While this incidence is perhaps unusually high in comparison with that found in some of the other studies, by reason of the nature of the clinical material available, it represents an index of the possible frequency of the disease. VonKaenel² studied a series of 3,000 consecutive autopsies at the St. Louis City Hospital—a general hospital—and found the incidence of gross evidence of cholecystitis to be 17.5 per cent. Thus there is considerable variation depending on the type of analysis made and the many factors involved. In some countries the lesion seems to be much less common. Again, cholecystitis is seen more frequently in persons possessing the sthenic and the hypersthenic body habitus. This

From the Department of Surgery, Washington University School of Medicine and Barnes Hospital.

1. Mentzer, S. H.: A Clinical and Pathologic Study of Cholecystitis and Cholelithiasis, Surg., Gynec. & Obst. **42**:782, 1926.

2. VonKaenel, J. E.: Personal communication to the authors.

is an old observation. While the exact significance of such an observation cannot be stated at present, it has been assumed to be related in a metabolic capacity.

Cholecystitis is relatively uncommon in children and in young adults (in whom bacterial inflammations are so often seen). There is a definite increase in the frequency of the disease with increasing age; it is much more prevalent in the fourth, the fifth and the sixth decades of life. It seems to bear but little association with ulcerative lesions of the intestinal tract and suppurative processes of the peritoneum, which are so often seen in younger people. If a bacterial invasion from the portal tract were the only pathogenic factor to be considered, one would expect a frequent association with such lesions. It is indeed questionable whether the triad of peptic ulcer, appendicitis and cholecystitis, stressed especially by Moynihan, is found with frequency enough to make it of any particular importance.

There is a decided preponderance of female over male patients. This fact, like that relating to body habitus, may have to do with altered metabolic processes, since these seem to be particularly concerned with the problem of cholelithiasis.

There is a definite relation between cholecystitis and cholelithiasis, despite the fact that stoneless cholecystitis is not infrequent. Seldom is cholelithiasis seen for any great length of time without pathologic changes in the wall of the gallbladder. While it is difficult to separate cause and effect in such instances, these changes sometimes differ strikingly from those produced by the presence of calculi in other organs. Stones in the gallbladder sooner or later may be concerned with either partial or complete obstruction of the cystic duct. The importance of this will be considered later.

Similarly, the pathologic picture seen in cases of cholecystitis is unique in many respects. Gangrene is not uncommonly observed with a patent cystic artery and abundant collateral circulation, both between the liver and the gallbladder and between the gallbladder wall and adjacent viscera. So profuse is the circulation between the wall of gallbladder and the liver that ligation of the cystic artery in the experimental animal produces no apparent circulatory damage. We have demonstrated this on numerous occasions. This disease therefore differs from gangrene of the common type seen in other portions of the body, in which arterial obstruction is the chief factor. It is highly suggestive of a direct action of some substance producing necrobiosis of the tissue.

Acute inflammation of the gallbladder is usually associated with gross and microscopic evidence of a preexisting chronic inflammatory process, i. e., with the fibrosis and the infiltration by cellular elements usually

associated with chronicity. It is rare to encounter an acute inflammatory process in the gallbladder in an area that has not been the seat of a preexisting inflammatory lesion.

In an area of acute cholecystitis the predominant pathologic feature is increased vascular permeability; there is also evidence of direct injury to tissue. The former presents itself chiefly as edema, extravasation of blood throughout the wall and monocytic infiltration with a relatively small amount of granulocytic invasion in proportion to the acuteness of the inflammation. The evidence of injury to tissue may be seen in definite necrotic areas, which often are irregularly distributed throughout the wall, and in fibrosis. In the early stage of the lesion these fibroblasts are young and edematous.

Acute cholecystitis unassociated with obstruction of the cystic duct is extremely rare. In an analysis of 508 cases Judd³ found that stone was present in the cystic duct in 484 of them (95.4 per cent). In a collection of 3,863 cases, Berk⁴ reported stone obstructing the cystic duct in 92.5 per cent of the cases. In the remaining small group the obstruction was usually due either to an inflammatory process or to a preexisting congenital anomaly as has been stressed by Seelig⁵ and by Gage.⁶

Often a specific inflammation may be seen in which the inciting factor is a lipid. This is more commonly observed in so-called cholesterosis of the gallbladder. Mild inflammation also is a constant finding in the gallbladder wall in which there is cholesterosis. Evidence of a deposition of bile or some of its components in the gallbladder wall may occasionally be seen in cases of chronic cholecystitis, as will be illustrated in this report.

EXPERIMENTAL OBSERVATIONS

From a consideration of the aforementioned features it seems justified to conclude that any causative agent able to effect such a pathologic syndrome as that seen in cholecystitis must have the ability to produce a particular injury to tissue, must have easy access to the gallbladder and must have its action increased with obstruction of the cystic duct. There must be present likewise a potentiality of modification during certain metabolic phases.

3. Judd, E. S., and Phillips, R.: *Acute Cholecystic Disease*, *Ann. Surg.* **98**: 771, 1933.

4. Berk, J. E.: *The Management of Acute Cholecystitis*, *Am. J. Digest. Dis.* **7**:325, 1940.

5. Seelig, M. G.: *Bile Duct Anomaly as a Factor in the Pathogenesis of Cholecystitis*, *Surg., Gynec. & Obst.* **36**:331, 1923.

6. Gage, M.: *The Surgery of Acute Cholecystitis*, New Orleans M. & S. J. **91**:607, 1939.

It occurred to us that bile might fulfil many of these qualifications and that it should be studied with the idea of its being a causative factor in the production or the instigation of cholecystitis. Some of these studies were recently recorded in a preliminary communication⁷ which will be expanded in this report.

Effect of Bile on Tissues.—That massive extravasations of bile into the peritoneal cavity are particularly injurious has long been recognized. Elaborate studies on the mechanism involved have been made particularly by Rewbridge⁸ and co-workers. This damage may or may not be associated with secondary bacterial invasion, although the latter is not uncommon, particularly in the peritoneal cavity, where the close proximity of the intestinal tract makes contamination more accessible. Again, a similarly destructive action of bile on tissues when there is a reflux of bile in the excretory ducts of the pancreas has long been observed. It is now a well established fact that when such a regurgitation takes place a series of changes occurs in the pancreatic tissue leading to tissue necrosis and hemorrhagic extravasation.

The action of bile on tissues is generally direct and apparently dependent on the concentration of the bile and on many of the different components of bile. The latter seem to be chiefly derivatives of cholic acid. When whole bile or any of these bile substances are injected into tissue, one of the earliest changes is a marked increase in vascular permeability as evidenced by edema. The transudation of plasma is often rapid and extensive and may be associated with diapedesis of red blood cells. Where the concentration of bile is greatest, actual necrosis quickly occurs. Granulocytic reaction is relatively slight, and most of the leukocytes present are of the monocytic series. One of the outstanding features is excessive and early fibroblastic proliferation. This is first seen at the periphery of the lesion, where the concentration of bile has not been so great. Such fibroblastic proliferation is in keeping with tissue reaction to steroids in general. Figure 1 illustrates some of the changes described.

Attention may be drawn to the fact that the reaction described is identical with that seen in different phases of clinical cholecystitis, namely, gangrene, edema, ecchymosis, round cell infiltration and fibrosis, depending on the severity of the involvement and the length of time the process has existed. These reactions likewise are subject to change by secondary bacterial invasion.

7. Womack, N. A., and Bricker, E. M.: Pathological Changes in the Gall-bladder Wall Due to the Action of Bile, *Proc. Soc. Exper. Biol. & Med.* **45**:710, 1940.

8. Rewbridge, A. G.: The Etiologic Role of Gas-Forming Bacilli in Experimental Bile Peritonitis, *Surg., Gynec. & Obst.* **52**:205, 1931.

Effect of Obstruction of the Cystic Duct.—We have previously referred to the frequency of the association of complete obstruction of the cystic duct with acute forms of cholecystitis. Since the two situations are almost universally found together, experiments were carried out to determine the importance of this relation.

(a) In 8 dogs, a curved cannula was inserted into the cystic duct and the bile aspirated from the gallbladder. The gallbladder was gently flushed with physiologic solution of sodium chloride, and an amount of this solution equivalent to the amount of bile withdrawn was left in the gallbladder. The cystic duct was ligated



Fig. 1.—Subcutaneous tissue of a dog two weeks after an injection of normal dog bile, showing the toxic effect of bile on tissue.

with fine silk at the point of injection. The animals were killed at different periods from one week to four months after operation. In 7 instances, the gallbladder was distended with mucus, and the wall was thin with no evidence of inflammation (fig. 2). In the other instance there was a purulent exudate in the lumen of the gallbladder, and the gallbladder wall showed evidence of acute inflammation. It would seem, therefore, that complete occlusion of the cystic duct without the presence of bile in the gallbladder results in distention with mucus unless it is associated with severe bacterial infection. In cases in which this is present, true empyema may supervene.

(b) The effect of complete obstruction of the cystic duct with the gallbladder bile left intact was next studied. Six dogs were used. There was slight variation in the results. Those dogs killed in the first few weeks showed a definite mild

subacute reaction. Those animals killed at the end of four months showed distention with mucus secretion and only slight fibrosis in the gallbladder wall. It was apparent that complete imprisonment of normal gallbladder bile in the dog was associated with moderate inflammatory change from which the organ could probably recover. It is well to bear in mind that in all probability the type of

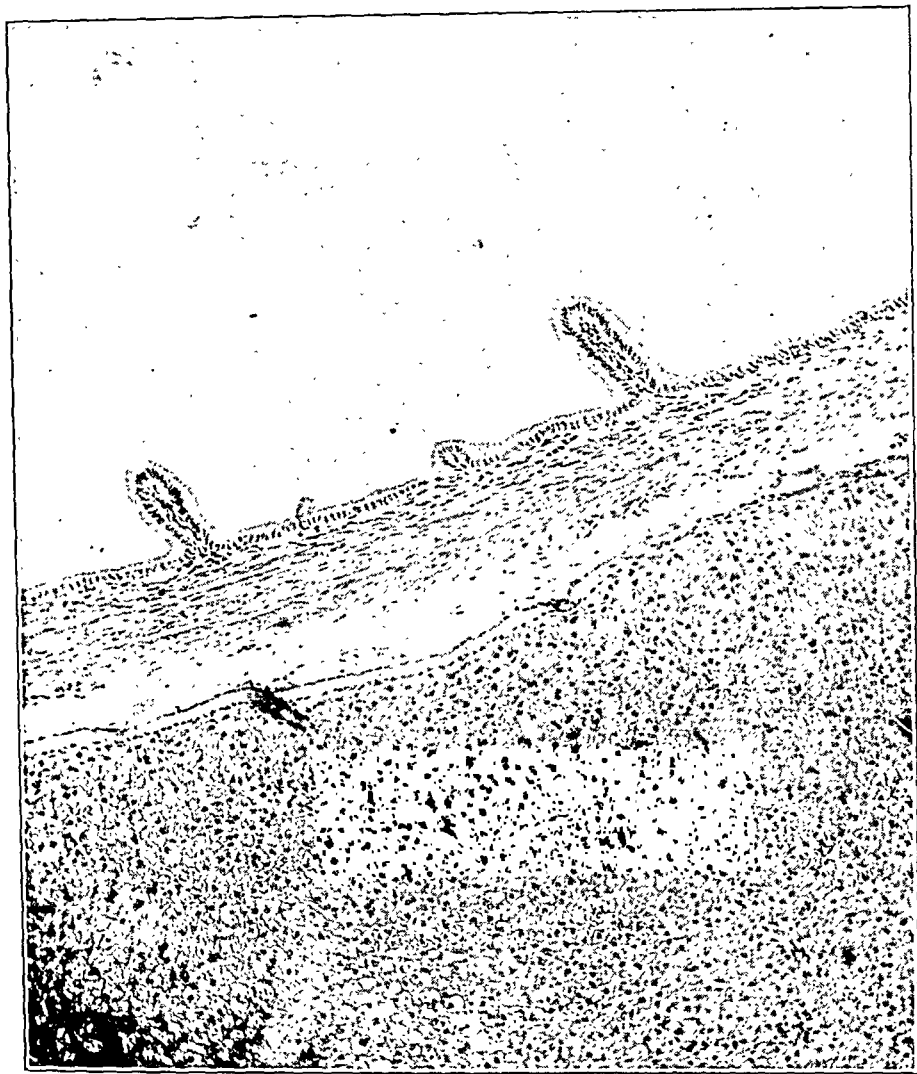


Fig. 2.—Gallbladder of a dog sixteen weeks after ligation of the cystic duct with replacement of the gallbladder bile by physiologic solution of sodium chloride. There is no demonstrable lesion in the gallbladder or the adjacent liver tissue.

reaction seen after such an experiment will vary in different animals according to the concentrating ability of the epithelium of the gallbladder and the nature of the bile peculiar to that species. In man many of the substances that we have found to be irritating to tissue are found in relatively high concentration, and furthermore the concentrating power of the gallbladder is excellent.

It is therefore probable that the tissue reaction described will be much more marked after cystic obstruction in the human being with bile of ordinary concentration.

(c) Because of the difference in the bile salt and the cholesterol content of dog's bile in comparison with human bile, studies were next carried out on the effect of imprisonment of concentrated dog's bile. Dog's gallbladder bile was concentrated to half its normal volume by extraction of its water at room temperature. After rapid evaporation, sterilization was assured by heating the bile for thirty minutes in a water bath; after this the bile was sterile on culture. There is no available evidence that heating at such a temperature produces any appreciable change in the chemical nature of the bile. Eleven dogs were used in the experiment. In 10 of them, a cannula was inserted in the cystic duct and the bile aspirated from the gallbladder. Concentrated bile prepared as described was reinjected into the gallbladder in an amount not quite equivalent to that withdrawn. The cannula was removed and the cystic duct ligated at the point of injection. In the remaining animal a fine needle was inserted in the fundus of the gallbladder, and through this the normal bile was aspirated and replaced with concentrated bile. The cystic duct was not disturbed.

The dog in which the cystic duct was not obstructed was killed at the end of two weeks. Both grossly and microscopically the gallbladder appeared normal (fig. 3A).

The remaining 10 dogs were killed at periods varying from twenty-four hours to four months. Those dogs killed in the first two days were killed at a time when they were obviously moribund. These animals all presented the same lesion, namely, one of gangrene of the gallbladder with severe hepatic injury but no evidence of peritonitis except a local adhesive type in the region of the gallbladder. The wall of the gallbladder was thickened owing to edema and hemorrhage in the wall and under the serosa. There was considerable necrosis with a minimal amount of polymorphonuclear infiltration. That portion of the liver adjacent to the gallbladder showed a similar change (fig. 3B). The picture in no way differed from that seen in acute cholecystitis in the human being. Vomiting, fever and leukocytosis were all present in the experimental animals.

Other animals apparently were able to withstand the damage produced and were killed at a later date (fig. 3C). They all showed the characteristic picture of chronic cholecystitis. In some animals in which this type of lesion was found the cystic duct was seen again to be patent. In 2 instances the lesions produced were much less marked. In 1 of these there was a mucocele, and in the other there was a precipitation of the bile solids in the form of many small soft stones. Whether the outpouring of mucus or the precipitation of stones represents a protective mechanism cannot be stated.

(d) To determine whether or not this bile action was nonspecific so far as species was concerned, the experiments were repeated with a solution of commercial dried bile.⁹ Distilled water was added to the powdered dried bile until the concentration was double that of normal gallbladder bile. Sterilization was obtained by placing the solution in a water bath for thirty minutes and was checked by culture.

The technic described in section c was now carried out. In 9 dogs, the bile was aspirated through the cystic duct, the dried bile solution reinjected and the

9. The solution of commercial dried bile (Desicol) for these experiments was supplied to us by the manufacturer, Parke, Davis & Co.

cystic duct ligated. In 3 dogs the gallbladder was aspirated through the fundus and the solution of commercial dried bile reinjected without manipulation or obstruction of the cystic duct.



Fig. 3.—The effect of dog's bile concentrated one time on the gallbladder wall: *A*, in a dog without obstruction of the cyst duct. Note the normal appearance one week later. *B*, in a dog with obstruction of the cystic duct. Note necrosis extending into the liver one week later. *C*, in a dog with obstruction of the cystic duct. One week later the reaction was not so severe as that shown in *B*.

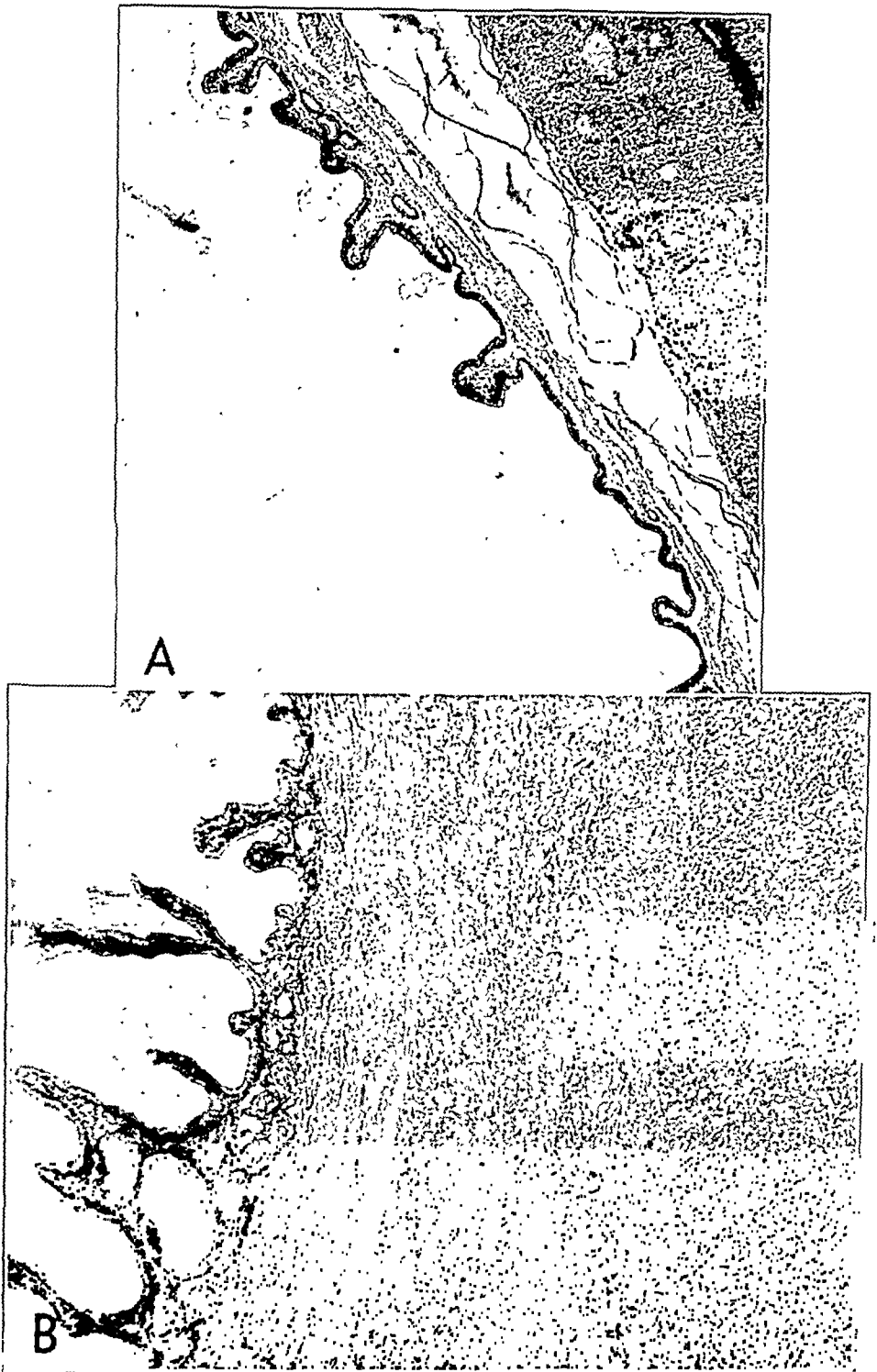


Fig. 4.—In this figure and in figure 5 the effect on the gallbladder of a solution of dried hog bile approximately equivalent to gallbladder bile concentrated one time: *A*, in a dog without obstruction of the cystic duct, one week after injection. Note normal gallbladder wall. *B*, in a dog with obstruction of the cystic duct, one week after injection.

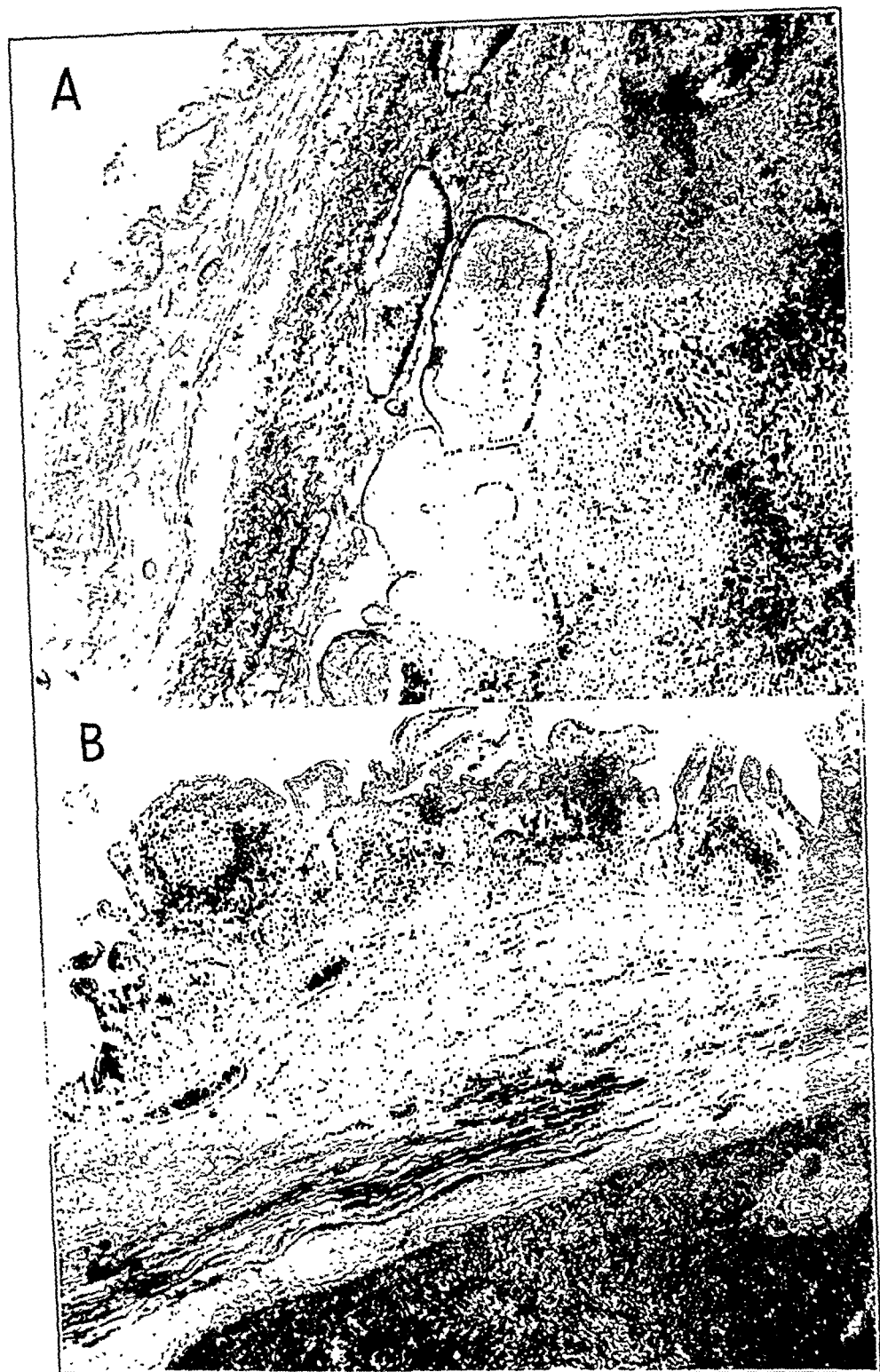


Fig. 5.—*A*, twenty-four hours after obstruction of the cystic duct. Note extensive gangrene with marked vascular dilatation. *B*, four weeks after obstruction of the cystic duct. Note the characteristic picture of chronic cholecystitis.

The animals were killed at intervals of twenty-four hours to five weeks. As we anticipated, the results were identical with those obtained when the dogs' bile was used in approximately the same concentration (figs. 4 and 5).

(e) We were now interested in establishing whether any particular component of bile is concerned with the production of this tissue damage. Evidence previously referred to already pointed to the fact that many of the bile steroids were capable of setting up just such an inflammatory reaction. In view of the fact that the composition of bile often differs somewhat in different species it was thought worth while to determine whether a similar change could be observed in relation to the gallbladder.

Because of the frequency with which cholesterosis of the gallbladder has been observed with the demonstration of cholesterol in the gallbladder wall, this substance was investigated first. Its well known action as a tissue irritant when present in such lesions as atheromatous plaques also was suggestive.

Accordingly, in 4 dogs, the bile was aspirated from the gallbladder through the cystic duct and replaced with an equal amount of cholesterol emulsion (1.3 per cent) in water. The cystic duct was ligated. Three other dogs were treated in a similar way; for these 2.6 per cent emulsion was used. Finally, in 8 dogs, the bile was aspirated from the gallbladder and used as a solvent for cholesterol crystals; the solution was then placed in the gallbladder through the cystic duct. Dog's bile usually contains only a relatively small amount of cholesterol, and as a result such solutions were easily prepared. Concentrations of cholesterol in bile varying from 1.5 to 5 per cent were used.

The animals were killed at intervals similar to those described in the previous experiments. The type of lesion found was generally speaking directly related to the concentration of the cholesterol. In cases in which concentrations over 3 per cent were used, necrosis of the gallbladder was frequent. In cases in which weaker concentrations were used, the picture of chronic cholecystitis was often observed to be in no way different from that in the human being. In cases in which the higher concentration was used, it was not unusual to observe degenerative changes in the liver, particularly notable around the periductal lymphatics.

Sodium desoxycholate and sodium glycocholate also were used. In a 3.5 per cent solution, the former produced such widespread necrosis that it did not lend itself well to experimentation. Often, particularly in rabbits, it was impossible to locate the gallbladder several days after the imprisonment of this substance. Conversely, sodium glycocholate was found to be the mildest of the substances used. Its effect, however, ran parallel to its concentration as did that of cholesterol.

Bacteriologic studies made in the course of these experiments have not been complete enough to warrant forming a definite opinion. Because the normal dog gallbladder and the liver so frequently show organisms, positive cultures were difficult to interpret. It is of interest to note that in 2 instances in which complete gangrene of the gallbladder was produced in a rabbit with deoxycholic acid, both aerobic and anaerobic cultures of the necrotic gallbladder wall were sterile.

Pathologic Evidence of Bile or Its Constituents in the Wall of the Gallbladder of Patients with Cholecystitis.—(a) Cholesterosis. This condition was recognized many years ago by Moynihan and given the name "strawberry gallbladder" by MacCarty, but its exact nature was

clearly shown by Boyd.¹⁰ He was able to demonstrate by chemical analysis as well as by specific staining methods that the mucosal and submucosal deposits, seen grossly as yellowish white spots, were either cholesterol or cholesterol esters. He was able to demonstrate chemically many times the normal amount of cholesterol in the gallbladder. He also noted that whenever the lipid was found in the gallbladder, it was always associated with evidence of chronic inflammation. Boyd did not care to express his opinion as to whether the inflammation was the



Fig. 6.—Cholesterol crystals in the wall of a human gallbladder.

cause or the effect. Sometimes when cholesterol esters are found in only slight amounts within histiocytes there may be a mild inflammatory reaction. At other times crystals of cholesterol may be found precipitated within the wall of the gallbladder as in figure 6. Whenever such a situation arises, there is generally a considerable amount of reaction, and often giant cells are found. In our opinion cholesterosis often represents an early phase of cholecystitis. While it can occur without the

10. Boyd, W.: *Surgical Pathology*, ed. 3, Philadelphia, W. B. Saunders Company, 1934.

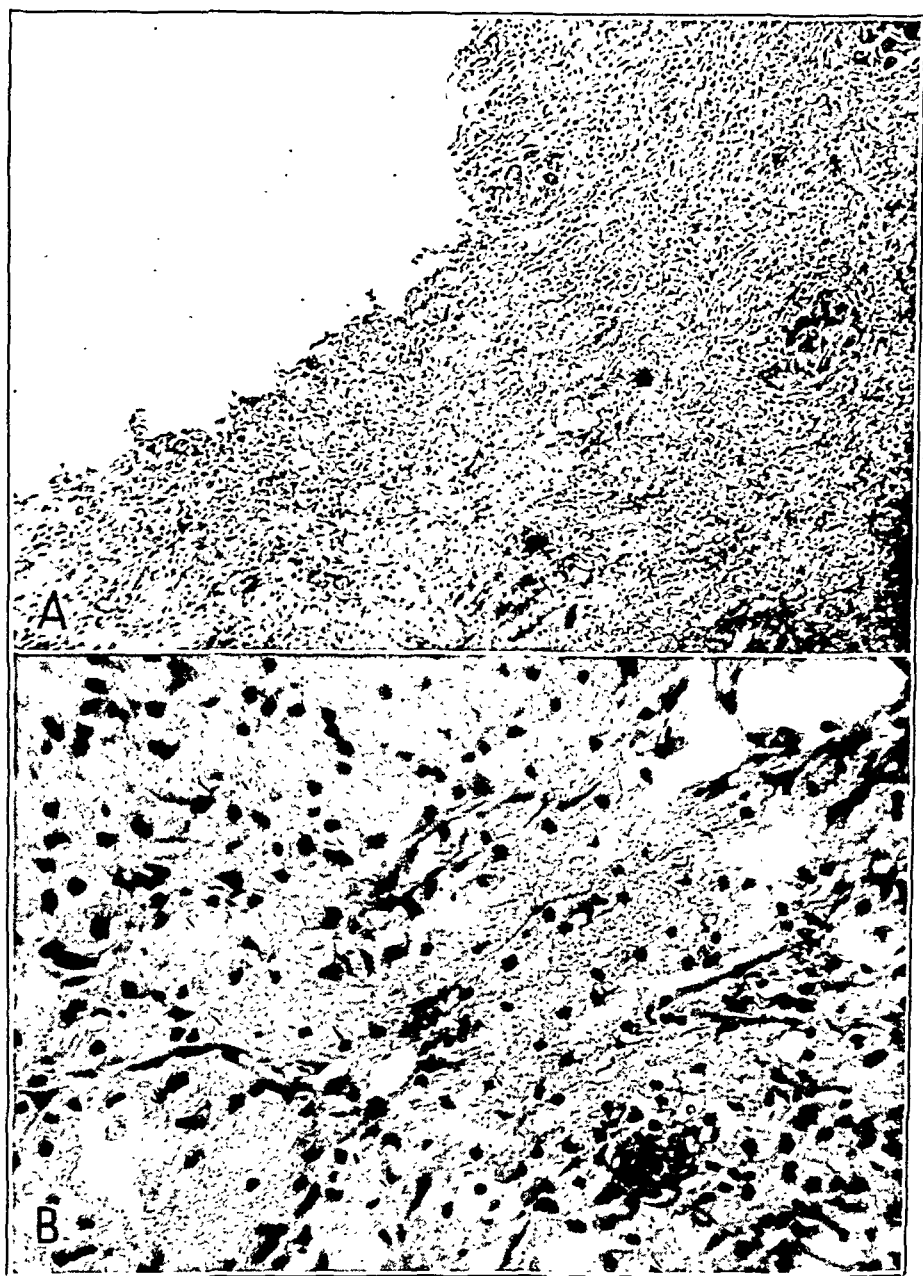


Fig. 7.—Histiocytes full of lipid in the wall of a human gallbladder, producing the picture of xanthomatosis: *A*, low power view; *B*, high power view.

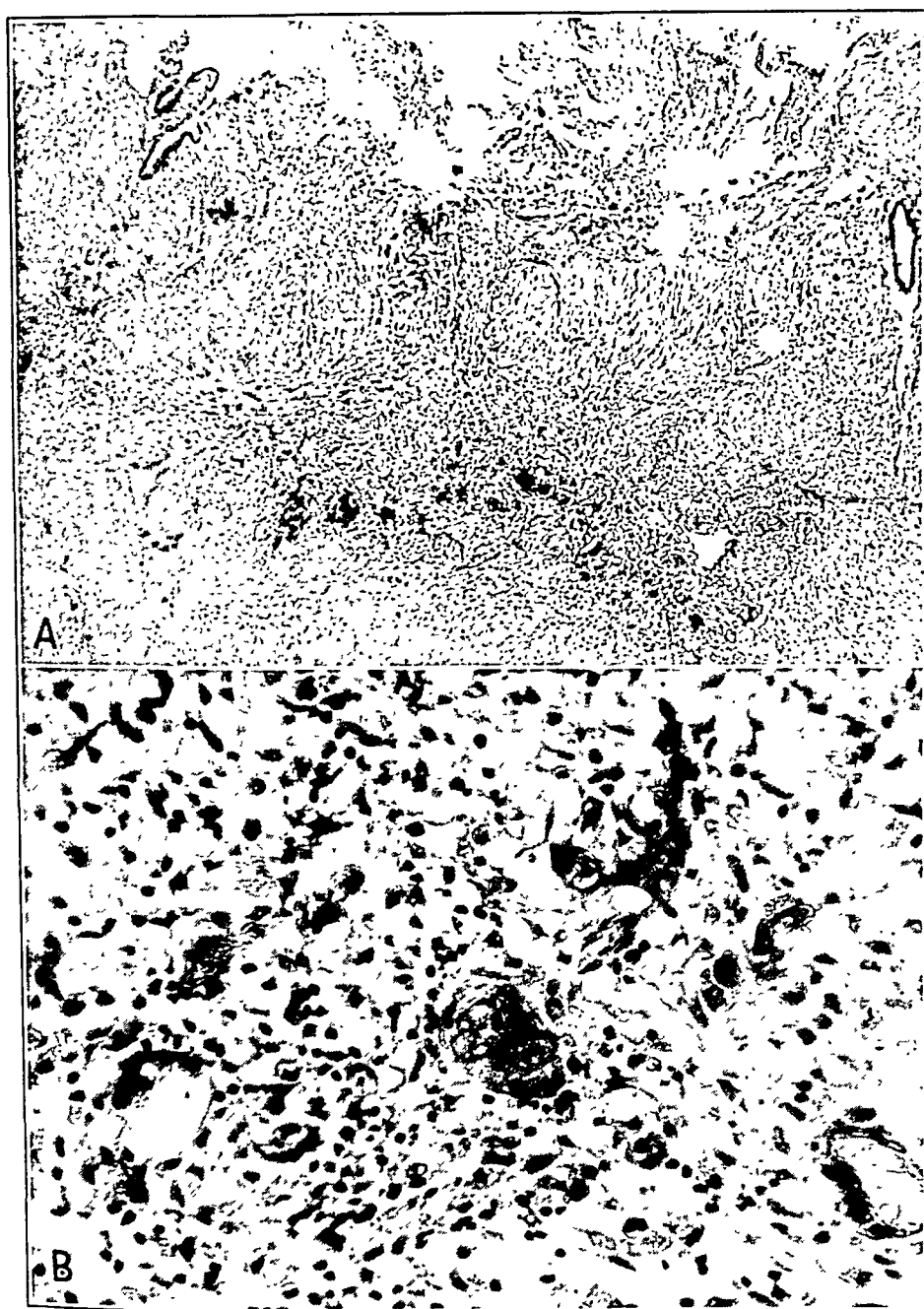


Fig. 8.—Inspissated bile in the wall of a human gallbladder: *A*, low power view; *B*, high power view. Note the type of cellular reaction and the edema present.

presence of stone, it is most frequently seen associated with cholesterol stones. Because its chemical nature can be identified, it probably represents the purest form of chemical cholecystitis seen in the human being.

(b) *Xanthomatosis of the Wall of the Gallbladder*: This is a lesion not often encountered. However, the demonstration of its presence at any time, it seems to us, is of considerable importance, for it is evidence of the fact that steroids, presumably from the bile, are found in the gallbladder wall and when present set up inflammatory reaction similar to that seen in cases of xanthomatosis elsewhere in the body. Figure 7 represents such a condition. It is interesting to notice that the epithelium of the gallbladder is completely destroyed in this area and that the wall of the gallbladder is infiltrated by histiocytes, the cytoplasm of which is swollen owing to ingested lipid. Here and there one sees islands in which there has been cellular breakdown with an associated giant cell reaction. It is possible that the lipid present in these cells is for the most part cholesterol in origin, but this we could not determine. It is important to stress the fact that the type of cellular reaction present here cannot, so far as we know, be produced by bacteria or by any form of irritant other than a lipid.

(c) *Bile in the Wall of the Gallbladder*: Much more frequently than is generally recognized it is possible to demonstrate what is apparently precipitated bile in the wall of the gallbladder. Since we have become interested in this question, we have been able to identify such a substance in many instances in which the gallbladder wall has been studied in cases of acute or subacute cholecystitis. Figure 8 represents a low and a high power view of such a situation. The dark opaque substances appear as a brilliantly yellow pigmented structure and differ in no way from inspissated bile seen in tissues elsewhere in the body. There is no evident crystallization, and the substance appears amorphous. It is interesting to note that the gallbladder shows a considerable loss of epithelium and that around the deposition of bile there is edema which is fairly well localized in some areas. There is likewise a cellular reaction, consisting of giant cells, histiocytes and lymphocytes. Early fibroblastic proliferation is also present. With the exception of cholesterosis, these types of chemical cholecystitis have been relatively rare in human beings. They were all associated with obstruction of the cystic duct, and all presented relatively marked inflammatory change of the gallbladder wall.

COMMENT

In considering the relation between these data and the causation of clinical cholecystitis, three factors may be considered to be of great importance: (1) obstruction of the cystic duct, either permanent or temporary, (2) the local damaging effect of imprisoned bile as a result

of either greater concentration or a difference in the bile constituents and (3) bacterial invasion, which generally is superimposed on injured tissue.

In our experiments, for the most part, we dealt with complete obstruction of the cystic duct. In many instances, however, in which an experiment was carried on for several months, it was found that the ligature had cut through the duct and that the lumen was again patent, allowing an ingress of hepatic bile into the gallbladder. The injury to the gallbladder wall, however, had already taken place. That complete obstruction of the cystic duct in the human being is frequently associated with inflammation of the gallbladder, which is often acute, has already been considered. That incomplete obstruction of the cystic duct will result in a less severe inflammatory reaction has recently been demonstrated by Cole and associates¹¹ in a convincing manner. By the production of partial occlusion of the cystic duct in dogs they found that after a number of months almost universally there were changes in the gallbladder wall identical with those seen in human beings with cholecystitis of a chronic sort. They were also able to show similar changes in the human gallbladder removed at operation in which developmental or anatomic defects were present interfering with the proper emptying of the concentrated gallbladder bile.

It is true that occasionally in cases of obstruction of the common duct due to cancer of the head of the pancreas or in the region of the ampulla of Vater, the gallbladder will be found to be greatly distended and appear to have a wall of relatively normal thickness. Actually, this is not so frequent as is generally assumed; the thinness of the wall is only apparent because of the distention. Microscopic studies of the gallbladder wall in such instances often show definite evidence of disease. When this is not present, it can easily be explained on the well demonstrated fact that on complete occlusion of the common duct secretion of bile from the liver ceases very quickly. This in turn leads to a lack of concentration of the bile due to several factors, the most important of which is the diluting action of the mucus and serum secreted by the gallbladder and the bile duct epithelium. We have frequently noticed that the secretion of mucus by the gallbladder epithelium acts to lessen the intensity of the inflammatory response to imprisoned concentrated bile in the gallbladder of the dog.

Perhaps the most common cause of obstruction of the cystic duct in the human being is cholelithiasis. Long-standing cholelithiasis is so universally associated with disease of the gallbladder wall that to find

11. Cole, W. H., and Rossiter, L. J.: The Relationship of Lesions of the Cystic Duct to Gallbladder Disease, *Am. J. Digest. Dis.* 5:576, 1938. Cole, W. H.; Hughes, E. O., and Novak, M. V.: The Relationship of Lesions of the Cystic Duct to the Pathogenesis of Cholecystitis, *Tr. Am. S. A.*, 1941, to be published.

a normal structure present is considered exceptional. Because of the difficulty of separating cause from effect, it is often impossible to evaluate accurately the part played by stone in the production of the lesion in an individual case. There are times, however, when the clinical evidence is suggestive. We have, for instance, observed soft pigment stones in the gallbladder of a child on whom splenectomy was performed for severe hemolytic jaundice of the familial type. There was moderate obstruction of the cystic duct due to precipitation within the folds, and the gallbladder wall presented the characteristic changes of well marked chronic cholecystitis. In those instances of cholesterosis with stone in which the gallbladder functions well with respect to the concentration of bile, gradual deterioration of this function can often be observed by the use of cholecystography. Instances likewise are encountered in which the classic clinical picture of biliary colic is found associated with normally concentrated bile. With the passage of time the gallbladder fails to be visualized by cholecystography, and at operation a diseased gallbladder wall is found with a minute stone imprisoned in one of the folds of the cystic duct.

No effort will be made here to consider those presumptive obstructions that appear to be due to failure of coordination of the neuromuscular mechanisms of the gallbladder and the bile ducts, which have been grouped under the term "dyskinesia." While the idea has been advanced that such lack of coordination might be the instigating factor in gallbladder disease, the evidence at the present time is not complete.

It seems apparent that interference with the ability of the gallbladder to empty itself adequately is concerned with the production of cholecystitis. Yet obstruction alone is not sufficient. As we have demonstrated, obstruction of an innocuous substance, such as physiologic solution of sodium chloride, does not result in inflammation. If an inflammatory change is to be produced, it is necessary that the obstructed substance be able to cause cellular damage. In our experiments we were able to demonstrate that bile was capable of doing this. Moreover the type of inflammation produced was in direct relation to the nature of the bile obstructed. It is well to bear in mind that the composition of bile is not constant. The type of bile salts present will often depend on the function of the liver, both as to its power of secretion and as to its power of detoxification. The latter function is related to the conjugation of bile salts with aminoacetic acid and taurine (aminoethylsulfonic acid). It is a clinical observation that frequently this function is seriously interfered with and that at such times the bile secreted may be much more injurious to tissue. We have seen several instances of acute noncalculous cholecystitis and cholangitis in which this apparently was the case. The bile factor therefore becomes a variable dependent on the composition and the concentration of the bile,

and the situation may and undoubtedly does exist in which it produces damage when there is no obstruction. In this connection it is of value to refer to one of the many brilliant experiments of Andrews and co-workers.¹² They were able to demonstrate that the injection of bile salts into the gallbladder results in acute inflammation even when there is no obstruction of the cystic duct.

It is possible that in instances of cholecystitis without apparent obstruction of the cystic duct local injury may also have been instigated by other substances than bile, for example, a reflux of pancreatic juice. This has been suggested by Wolfer¹³ and by Bisgard,¹⁴ both of whom presented evidence that pancreatic juice introduced into the gallbladder can produce serious destructive changes as it does in other tissues when it is activated.

The third factor to be considered in the production of cholecystitis is that of infection. The evidence that there is actual bacterial invasion in many cases of cholecystitis has been so incontrovertible that any other explanation of the pathogenesis has been considered unlikely by many. As we have stated earlier, however, there are many clinical and pathologic features about cholecystitis incompatible with such a simple interpretation. These features are provided for by the inclusion of the obstructive and the chemical effects already discussed. This is by no means meant to exclude the action of bacteria. Such an effect is complementary and necessary to explain the entire picture.

Considerable attention has been focused on the fact that in cases of cholecystitis bacteria are often found in the gallbladder wall and less frequently in the contents of the gallbladder. Much less attention has been given to the fact that often no organisms are found. Actually this is true in a considerable group of cases. In approximately two thirds of the cases, the gallbladder bile is sterile, while in about one third the wall of the gallbladder is sterile. The significance of this fact was not appreciated until similar studies were made on the number and the type of bacteria found in the wall and the bile of the normal human gallbladder.

In a recent communication, Andrews and Henry¹⁵ were able to demonstrate that both quantitatively and qualitatively there was but little difference in the cultures of gallbladders of all types, including those with acute inflammation and those that were microscopically normal. In many instances of acute cholecystitis they encountered a

12. Aronsohn, H. G., and Andrews, E.: *Experimental Cholecystitis*, Surg., Gynec. & Obst. **66**:748, 1938.

13. Wolfer, J. A.: *The Role of the Pancreatic Juice in the Production of Gallbladder Disease*, Surg., Gynec. & Obst. **53**:443, 1931.

14. Bisgard, J. D., and Baker, C. P.: *Studies Relating to the Pathogenesis of Cholecystitis, Cholelithiasis and Acute Pancreatitis*, Tr. Am. S. A. **58**:572, 1940.

15. Andrews, E., and Henry, L. D.: *Bacteriology of Normal and Diseased Gallbladders*, Arch. Int. Med. **56**:1171 (Dec.) 1935.

gallbladder the wall and the contents of which were both sterile. We have had a similar experience. The facts, then, that an acute inflammatory process can be present in a gallbladder sterile to culture and that a rich flora can be obtained from a normal gallbladder make one hesitate to place too much emphasis on the conception of cholecystitis as simply and purely a bacterial infection.

Several years ago in a series of contributions Graham and co-workers presented evidence to prove that cholecystitis could be produced by bacterial invasion and that this invasion was probably lymphogenous in type and certainly associated closely with a similar process in the hepatic periductal areas, particularly those in the neighborhood of the gallbladder. In one of their contributions¹⁶ they called attention to the fact that if the gallbladder wall is injured, bacterial infection is much easier to produce. It is this factor of injury, however slight, that so often initiates infection. Subsequently, the infectious process may be so severe that the factor of injury is overlooked. It is none the less important. This is a rule with few exceptions wherever infection may occur in the human body. In cases of cholecystitis the way in which such injury may occur is, as we have shown, inherent in the biliary mechanism. If the frequency of the presence of bacteria in the normal liver and the gallbladder be kept in mind, the origin of the infectious picture in cases of cholecystitis becomes apparent. Bacteria are not necessary as a factor in the production of the condition, but rather they are to be regarded as a complication in the history of the lesion that may be of great importance.

SUMMARY AND CONCLUSIONS

Experimental evidence is presented to demonstrate that in dogs complete obstruction of the cystic duct does not produce inflammation of the gallbladder wall if the imprisoned bile is replaced with physiologic solution of sodium chloride.

Complete obstruction of the cystic duct by which bile is left imprisoned in the gallbladder results in inflammation the severity and type of which are in direct proportion to the content and the concentration of the bile obstructed. This inflammation is identical with that encountered in clinical cholecystitis. Evidence is submitted to show that this inflammation is produced by the direct action of bile on tissue and that bile and its components can be demonstrated at times in the wall of the gallbladder in cases of human cholecystitis.

Bacterial infection may or may not be present. While bacterial infection may at times be of great clinical importance, from the standpoint of pathogenesis it should be considered as a complication that results when contaminated tissue is injured.

16. Graham, E. A., and Peterman, M. G.: Further Observations on the Lymphatic Origin of Cholecystitis, *Arch. Surg.* 4:23 (Jan.) 1922.

GANGRENE AND PERFORATION OF THE WALL OF THE GALLBLADDER

A SEQUELA OF ACUTE CHOLECYSTITIS

FRANK GLENN, M.D.

AND

S. W. MOORE, M.D.

NEW YORK

Almost a century ago (1844), James Duncan,¹ surgeon at the Royal Infirmary in Edinburgh, reported an instance of gangrene of the gallbladder which had ruptured, producing peritonitis, followed by death. The diagnosis was made at autopsy. In 1933, Dr. Samuel A. Vest Jr.,² of Baltimore, collected the reported cases of gangrenous cholecystitis; a total of 71 were gleaned from the literature, and 9 were reported as new. Twenty-three of the 80 patients died as a result of the condition—a mortality rate of 37 per cent. Gangrene of a portion of the entire wall of the gallbladder is, we believe, a sequela of acute cholecystitis and frequently leads to perforation.

By "gangrene of the wall of the gallbladder" we refer to complete necrosis of a portion of the wall in one or more areas; we do not use the term to indicate gangrene of the entire gallbladder. Our reason for this is based on the frequent observation that a single area of gangrene of the wall of the gallbladder results in perforation, as may gangrene of the entire organ. Perforation of the gallbladder is usually followed by grave complications and sometimes death. The high incidence of gangrene in patients who have acute cholecystitis has led us to record our observations of a group of patients who at operation were found to have gangrene of the wall of the gallbladder. Because one of the serious complications is perforation, we have reviewed our material carefully in search of the mechanism involved in this process.

The mechanism whereby perforation takes place in acute cholecystitis is of interest not only to the pathologist but to the surgeon and the physician. Gangrene of the wall of the gallbladder is often the result

From the Department of Surgery of the New York Hospital and Cornell University Medical College.

1. Duncan, J.: Femoral Hernia: Gangrene of the Gall Bladder; Extravasation of Bile; Peritonitis; Death, *North. J. Med.* **2**:151-153, 1844-1845.

2. Vest, S. A., Jr.: Gangrene of the Gallbladder, *Internat. S. Digest* **15**:131-160, 1933.

of changes that take place in the organ during an attack of acute cholecystitis. The findings most frequently encountered at operation are a stone impacted in the ampulla of the gallbladder, edema of the wall thus encroached on, blockage of the lymphatics, obstruction to the venous return by direct pressure on the vessel or by thrombosis and in some instances arterial occlusion. Probably no one process accounts for all perforations. For this reason we wish to call attention to another mechanism which we believe accounts for a fair proportion of perforations of the gallbladder. We consider that this process is closely associated with circulatory changes and infection, which play an important role.

The gallbladder resembles the intestinal tract in that as an organ it is a hollow viscus lined with mucous membrane supported on a wall

TABLE 1.—*The Incidence of Rokitansky-Aschoff Sinuses in Cases of Acute Gangrenous Cholecystitis*

Gangrene of the wall of the gallbladder.....	59
Number containing Rokitansky-Aschoff sinuses.....	30
Mucosa completely destroyed.....	15
No Rokitansky-Aschoff sinuses seen.....	14
Gangrene of the wall of the gallbladder with perforation.....	22
Number containing Rokitansky-Aschoff sinuses.....	15
Mucosa completely destroyed.....	3
No sections taken.....	1
No Rokitansky-Aschoff sinuses seen.....	3
Gangrene of the wall of the gallbladder with free perforation.....	3
Mucosa completely destroyed.....	2
Rokitansky-Aschoff sinuses seen.....	1

of submucosa and muscle and incompletely covered by peritoneum. Defects in the supportive structure of the intestinal tract in the presence of increased pressure within the viscus may result in protrusion of the mucosa through the defects in the wall. Examples are found in diverticula of the esophagus, duodenum and large bowel. The part played by the physical force of increased pressure within a viscus and diminished resistance in the structure of the wall is best seen in the large bowel of the aged patient with multiple diverticula. A similar process, we believe, takes place in the gallbladder. The early manifestations of diverticula of the wall of the gallbladder were recognized by Rokitansky,³ who first described those diverticula and compared them with diverticula in the gastrointestinal tract. Aschoff⁴ also considered these

3. von Rokitansky, C.: *A Manual of Pathological Anatomy*, translated by E. Sieveking, Philadelphia, Blanchard & Lea, 1855, vol. 2, p. 130.

4. Aschoff, L.: *Bemerkungen zur pathologischen Anatomie der Cholelithiasis und Cholecystitis*, *Verhandl. d. deutsch. path. Gesellsch.* 9:41-48, 1905.

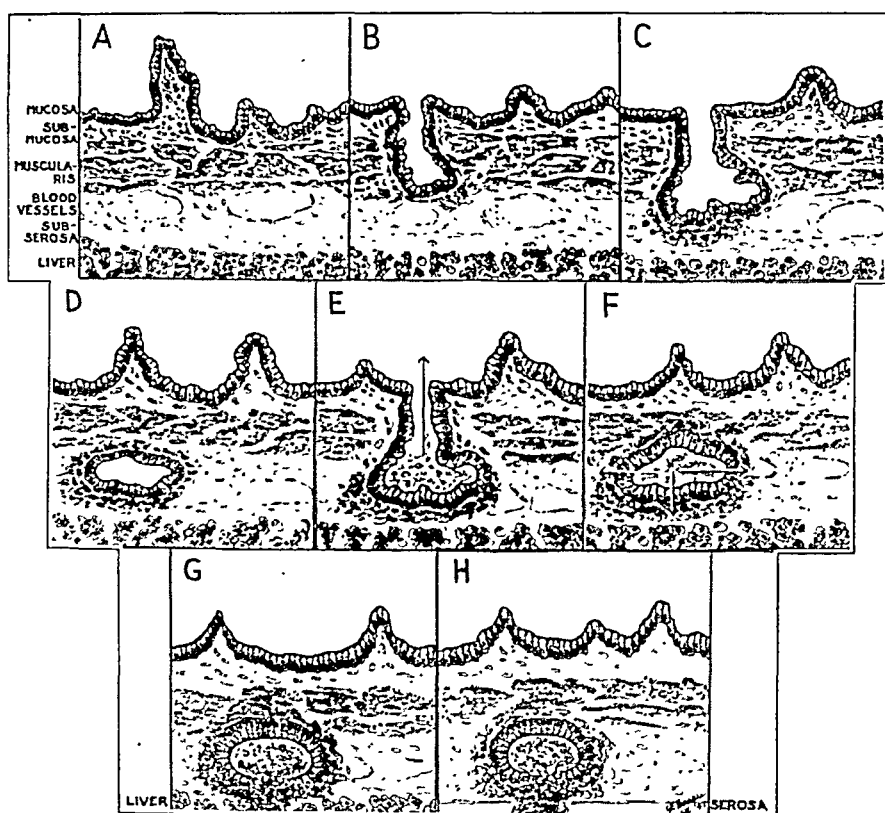


Fig. 1.—The wall of the normal gallbladder includes a mucosa of columnar epithelium on a muscular layer rich in elastic fibers supported by a strong tunica muscularis formed chiefly of bundles which have a circular direction (*A*). Where the gallbladder is covered by peritoneum, there is also a serous coat.

Throughout the gallbladder wall there are folds of mucous membrane that form crypts which are variable and often of considerable depth. When these crypts or sinuses completely penetrate the muscularis as described by Rokitansky and later by Aschoff, they are designated Rokitansky-Aschoff sinuses (*B*). With increased intracystic pressure and diminished resistance in the wall, this crypt may become branched to form a diverticulum and extend beneath the muscularis (*C*). On section such a diverticulum may appear to have no communication with the lumen of the gallbladder owing to the extension beneath the muscularis (*D*). However, if several sections are made, the communication may be traced. In a diverticulum of this type an abscess may form. If the abscess increases, it may empty either through its original channel into the gallbladder (*E*), or it may extend in the line of least resistance within the wall of the gallbladder (*F*).

Such an abscess may rupture into the liver (*G*).

An abscess in that portion of the gallbladder which is covered by peritoneum may rupture into the peritoneal cavity (*H*).

The mechanism is probably much more complicated than is shown in this schematic presentation. It is likely that impaired circulation in the presence of infection may result in numerous perforations within a comparatively small area of the gallbladder wall. We believe that rupture into the liver substance occurs frequently, while perforation into the serosa and the free peritoneal cavity is rare.

diverticula in the same light. Sinuses are frequently present in the walls of infected gallbladders. It is believed that these sinuses are enlarged and increased by forceful contractions of the organ and that in one or more the mucosal layer is forced through the supporting structure of the wall of the gallbladder to become branched with a small neck communicating with the inner aspect of the organ. The frequency of the occurrence of these sinuses was demonstrated in a review by one of us (Moore⁵); 300 gallbladders removed at operation were examined and 101, or one third, were observed to have recognizable Rokitansky sinuses. Ninety-seven per cent of these gallbladders contained stones.

When a simple sinus becomes a branched diverticulum with a small neck, changes within the wall of the gallbladder or within the sinus itself may result in occlusion of this outlet. Such conditions arise during the change in the wall associated with acute diffuse inflammation of the gallbladder, obstruction of the cystic duct and impairment of the circulation of the lymphatic drainage. With any of these, a Rokitansky-Aschoff sinus which has developed into a diverticulum and then undergone occlusion becomes a potential abscess. If the gallbladder contains bacteria, the occluded Rokitansky-Aschoff sinus also probably will, and thus the abscess increases and extends as a result of the bacterial action. As the small abscess increases in size, it extends in the line of least resistance, which is usually toward the periphery. If the periphery is covered by peritoneum, a sufficient degree of resistance may be encountered to prevent rupture. If, however, there is no peritoneum, as in the hepatic portion of the gallbladder, perforation through the wall takes place rather rapidly. The abscess, no longer confined within the gallbladder wall, may extend between the gallbladder and the liver or through the liver to form a subphrenic abscess. If the process is sufficiently rapid, perforation through the peritoneal surface of the gallbladder may take place. This would, of course, be a free perforation into the peritoneal cavity, were it not for the high efficiency of the omentum and the regional viscera, which tend to wall the abscess off as soon as perforation becomes imminent.

The association of the Rokitansky-Aschoff sinus with long-standing infection and calculi in the gallbladder proper and the rarity with which perforation of the gangrenous gallbladder wall occurs when infection and calculi have not preexisted indicate that such a mechanism may frequently be involved. Furthermore, such a mechanism could account for the multiple perforations of the gallbladder which are occasionally encountered.

5. Moore, S. W.: Intramural Formation of Gallstones, *Arch. Surg.* **34**:410-423 (March) 1937.



Fig. 2.—*A*, photomicrograph ($\times 97$) of an artery in the wall of a gallbladder showing thrombosis with invasion of the thrombus by polymorphonuclear leukocytes. *B*, photomicrograph ($\times 110$) of an artery with an organized thrombus and recanalization. We interpret this as the end process of that shown in *A*.

Gangrenous cholecystitis has been observed to occur after unrelated surgical operations. A case was reported by Kocher,⁶ in which acute cholecystitis developed in a 51 year old woman eight days after repair of a ventral hernia. In another case, reported by Duncan, the condition followed operation on a woman with strangulated femoral hernia and intestinal obstruction. The patient died, and postmortem examination showed a gangrenous perforated gallbladder with generalized biliary peritonitis. No stones were found. W. A. Fisher⁷ reported the case of a 19 year old football player who was operated on for reduction of the scaphoid bone. Acute gangrenous cholecystitis developed two days later. No stones were found, and he recovered. One of us (Glenn) recently saw a patient in whom gangrenous cholecystitis developed with free perforation five days after operation for hydrocele.

Gangrene of the gallbladder is not unusual and occurs far more frequently than one is generally disposed to assume. Over a period of slightly more than eight years we have observed in the New York Hospital 84 patients on whom a diagnosis of gangrene of the wall of the gallbladder according to the aforementioned definition was made. By and large, this condition has been accurately diagnosed under the general term of acute cholecystitis. In this period almost 350 patients were subjected to surgical treatment for acute cholecystitis. Preoperatively, it is probably impossible to differentiate acute cholecystitis, empyema of the gallbladder and gangrene of the gallbladder. The clinical manifestations of a progressive process are sometimes entirely lacking. Examples have been encountered in which a patient over 50 years of age has had only slight elevation of temperature and minimal leukocytosis with a palpable mass in the right upper quadrant of the abdomen but at operation has been found to have a gangrenous gallbladder.⁸ On the other hand, it has been more frequently observed that when the patient's temperature rises and the leukocyte count increases during a period of observation, at operation progressive gangrene of this organ is found.

In this series of 84 patients with gangrene of the gallbladder wall there are 44 women and 40 men—a far higher incidence among men than is noted with regard to the general occurrence of the disease, for in a series of almost 1,500 patients subjected to operation for nonmalignant disease of the biliary tract the ratio was 1 man to 4-5 women. The gallbladders of 5 of these men did not contain calculi, while calculi were found in the gallbladders of all the women. One of the 5 men was operated on some three years later, and a stone was removed from

6. Kocher, T., and Matti, H.: Ueber 100 Operationen an den Gallenwegen mit Berücksichtigung der Dauererfolge, *Arch. f. klin. Chir.* **81**:655, 1906.

7. Fisher, W. A., cited by Vest.²

8. Glenn, F.: Acute Cholecystitis, *Surg., Gynec. & Obst.* **69**:431-435, 1939.

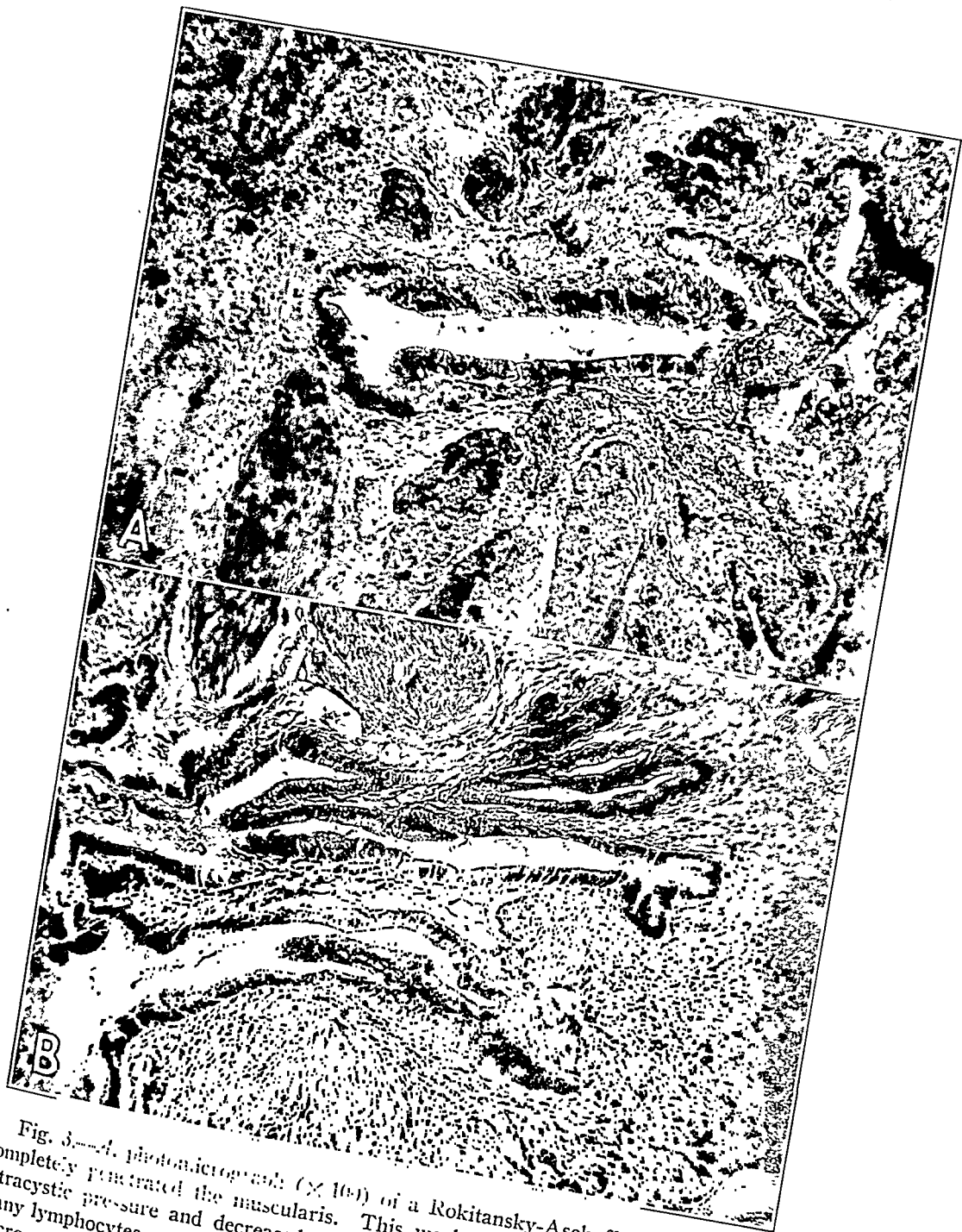


Fig. 3.—4. photomicrograph ($\times 100$) of a Rokitansky-Aschoff sinus which has completely penetrated the muscularis. This we believe is the result of increased intracystic pressure and decreased resistance in the gallbladder wall. There are many lymphocytes, suggestive of the degree of inflammation in this area. B, photomicrograph ($\times 78$) of the mucosa of the lumen of a gallbladder continuous with a Rokitansky-Aschoff sinus which has penetrated the muscular layer.

the common duct. It might be assumed in this particular instance that the gallbladder contained small stones which passed into the common duct. Forty of the 44 women had undergone one or more pregnancies. The youngest patient was 9 and the oldest 73. In the majority of instances gangrene of the wall of the gallbladder occurred after the beginning of the fifth decade. Of the total of 84 patients there were 59 who had symptoms of gangrene of the wall of the gallbladder without evidence of perforation. In the majority of these, however, the omentum, as well as the adjacent viscera, had become adherent to the organ. In 22 patients there was perforation with localized peritonitis or localized abscess. There were many instances in which there were multiple gangrenous areas of the gallbladder with more than one perforation. These perforations resulted in abscess between the gallbladder and the liver, between the gallbladder and the omentum and also the viscera. There was 1 instance of perforation into the transverse colon and the duodenum. There were 3 patients with free perforation into

TABLE 2.—*Average Age of Eighty-Four Patients with Acute Gangrenous Cholecystitis*

Patients		Condition	Average Age
3	Free perforations		56
22	Perforations and abscess.....		50
59	Gangrenous cholecystitis		44

the peritoneal cavity. Two of these patients died, whereas only 3 of the remaining 81 patients died.

The purpose of reporting this series of patients with gangrene of the wall of the gallbladder is to emphasize the advisability of the surgical treatment of the patient with acute cholecystitis. In a review of our total experience with this disease we have concluded that we are unable to distinguish acute cholecystitis, acute cholecystitis with gangrene and perforation which has resulted in a walled-off abscess. Free perforation into the peritoneal cavity of a gangrenous gallbladder is rarely recognized early enough to save the patient's life; this is evidenced in 3 patients in whom we found free perforation and among whom the mortality rate was 66 per cent.

One of the deaths reported in this series was that of a child with typhoid fever. The removal of the gangrenous gallbladder unfortunately did not favorably influence the course of the disease, and it is probable that the removal of the gallbladder had little to do with the peritonitis from which the patient died. Fortunately, typhoid fever is rare in this era and therefore should probably not be considered in this series of patients. A 41 year old patient died on his sixth postoperative day from pneumonia. This death is to be credited to the operative pro-



Fig. 4.—*A*, photomicrograph ($\times 97$) of a thin gallbladder wall which contained a tremendously dilated Rokitsansky-Aschoff sinus that had penetrated the muscularis. This sinus contained an intramural gallstone. That it is lined with mucosa is demonstrated in *B*, a higher magnification ($\times 331$).

cedure and not to the course of the disease, although this patient might have continued on to free perforation and peritonitis. A third patient, a 50 year old woman, had neglected gangrenous cholecystitis with perforation and localized peritonitis which had extended to become a sub-diaphragmatic abscess. Perforation through the diaphragm into the pleural cavity resulted in empyema and death. Earlier operation would have prevented this unfortunate course of events. The remaining 2 deaths were those of patients with free perforation and generalized peritonitis; 1 was 50 years of age and the other 65. These 2 patients represent the group in which free perforation is most likely to occur. Thus, acute cholecystitis in patients over 50 at once becomes a more serious disease than acute cholecystitis in patients under 50. If one is to employ surgical therapy for patients under the age of 50, then it should be urged much more forcefully for those over 50, because it is in this group that perforation and free perforation are most likely to occur. It is these complications that carry with them the highest mortality rate.

The treatment of acute cholecystitis with gangrene does not differ from that of acute inflammation of the gallbladder. It is advisable to remove the gallbladder, provided the patient's general condition and local complications do not contraindicate such a procedure. In this series of patients, 77 were subjected to cholecystectomy, 6 to cholecystostomy, and 1 patient was not operated on. Cholecystostomy is generally reserved for those patients in whom cholecystectomy is contraindicated. Therefore, these patients are the more ill, and the associated high mortality rate is indicative of the severity of the disease rather than of the risk of the type of procedure employed.

The differential diagnosis between biliary colic, acute cholecystitis and other acute conditions commonly found in the right upper quadrant of the abdomen taxes the diagnostic acumen of the most experienced abdominal surgeon. Because perforated ulcer, acute appendicitis or acute pancreatitis may lead to death if surgical intervention is withheld, a differential diagnosis appears less important than an attitude which leads to surgical treatment. Without an attitude that provides for the surgical treatment of acute cholecystitis there may be justification for both practitioner and surgeon to permit certain of these acute abdominal conditions to progress into their terminal phase without operation. Perhaps free perforations into the peritoneal cavity following acute cholecystitis occur because a policy of operating on all patients is not more generally held. Zollinger⁹ has correctly insisted that each patient with acute cholecystitis should be considered as an individual surgical problem. With this we agree, for all surgical problems are such.

9. Zollinger, R.: Acute Cholecystitis, *New England J. Med.* **224**:533-537, 1941.

DUPUYTREN'S CONTRACTURE

A CONSIDERATION OF THE ANATOMY OF THE FIBROUS STRUCTURES OF
THE HAND IN RELATION TO THIS CONDITION, WITH AN
INTERPRETATION OF THE HISTOLOGY

THOMAS HORWITZ, M.D.*

PHILADELPHIA

The material of the present study has been evaluated under three headings: (1) the gross anatomy of the human palmar fascia as revealed in a study of 60 hands presenting no gross abnormality of this structure; (2) the microscopic anatomy of the palmar fascia in 27 grossly normal hands, and (3) the histology of the tissue removed in 35 cases of Dupuytren's contracture.

GROSS ANATOMY OF THE NORMAL HUMAN PALMAR FASCIA—ITS RELATION TO THE DEVELOPMENT AND THE SURGICAL COR- RECTION OF THE DEFORMITY IN DUPUYTREN'S CONTRACTURE

The material consisted of 60 hands from 30 cadavers of men between 22 and 85 years of age. It was felt that the anatomic descriptions should include not only the superficial palmar layer and its attachments but also the deep interosseous fascia and the interfascial septums. All of these structures bear an intimate relation, proximally, to the fascial structures of the volar surface of the wrist and the forearm, and, distally, to the fascial and ligamentous structures of the fingers. As emphasized by Kanavel, Koch and Mason,¹ these anatomic facts have an important bearing on the development and the surgical correction of the deformity in Dupuytren's contracture.

In the material studied it was found that the superficial palmar fascia merged, proximally, with the palmar surface of the transverse carpal ligament and with the tendon of the palmaris longus muscle or, in

*Corinna Borden Keen Research Fellow of Jefferson Medical College of Philadelphia.

From the Daniel Baugh Institute of Anatomy, Jefferson Medical College of Philadelphia (Dr. J. Parsons Schaeffer, director) and the Laboratories of Pathology, Hospital for Joint Diseases, New York (Dr. Henry L. Jaffe, director).

1. Kanavel, A. B.; Koch, S. L., and Mason, M. L.: Dupuytren's Contraction, with a Description of the Palmar Fascia, a Review of the Literature and a Report of Twenty-Nine Surgically Treated Cases, *Surg., Gynec. & Obst.* **48**:145-190, 1929.

the absence of the latter, with the antebrachial fascia. Distally, its longitudinal fibers broke up into longitudinal bands (the pretendinous bands). Fibers extended into the deep surface of the skin along the entire length of the pretendinous bands and were especially developed over the region of the metacarpophalangeal joints. A thin fascial extension covered the interdigital spaces in which the digital nerves and vessels became more superficial. Between these distinct bands there were deeper, intertwining transverse fibers which became most distinct in the region of the distal transverse palmar crease and again in the region of the finger webs (the natatory ligaments). These transverse fibers were found to be intimately attached to the fibrous tendon sheaths of the fingers and to the deep surface of the overlying skin. Laterally and medially, the superficial palmar fascia thinned out where it overlay the thenar and hypothenar muscle groups (fig. 1).

The number and the arrangement of the pretendinous bands varied considerably. This variation was demonstrated by Kalberg² in an extensive series of 400 palmar fascia specimens (234 from the right hand, 166 from the left). He found that the number and the arrangement of the pretendinous bands varied as follows:

- Three bands in 2 per cent of the specimens to the second, third and fifth fingers
- Four bands in 24 per cent of the specimens to the second, third, fourth and fifth fingers
- Five bands in 18 per cent of the specimens to the first, second, third, fourth and fifth fingers
- Five bands in 31 per cent of the specimens—single bands to the third, fourth and fifth fingers; double band (split) to the second finger
- Six bands in 14 per cent of the specimens—single bands to the third and fifth fingers; double bands (split) to the second and fourth fingers
- Seven bands in 11 per cent of the specimens—single bands to the first, third and fifth fingers; double bands to the second and fourth fingers

Fibers from the deep surface of each longitudinal band merged with the fibrous sheath of the flexor tendons and could be traced for a variable distance along the superficial layer of the sheath as far distalward as the middle phalanx. The latter portions of each longitudinal band formed two distinct lateral bands at the webs, which gained attachment to the sides of the flexor tendon sheaths, to the capsule of the metacarpophalangeal joint and to the periosteum of the proximal phalanx and which were intimately related to the aponeurotic expansion of the extensor tendon and to the insertion of the interosseous and lumbrical muscles.

The volar interosseous fascia covered the palmar interosseous muscles and communicated with the superficial fascial layer by vertical septums which formed the fascial compartments of the hand. Proximally,

2. Kalberg, W.: Zur Anatomie der Palmaraponeurose, *Anat. Anz.* **81**:149-159, 1935.

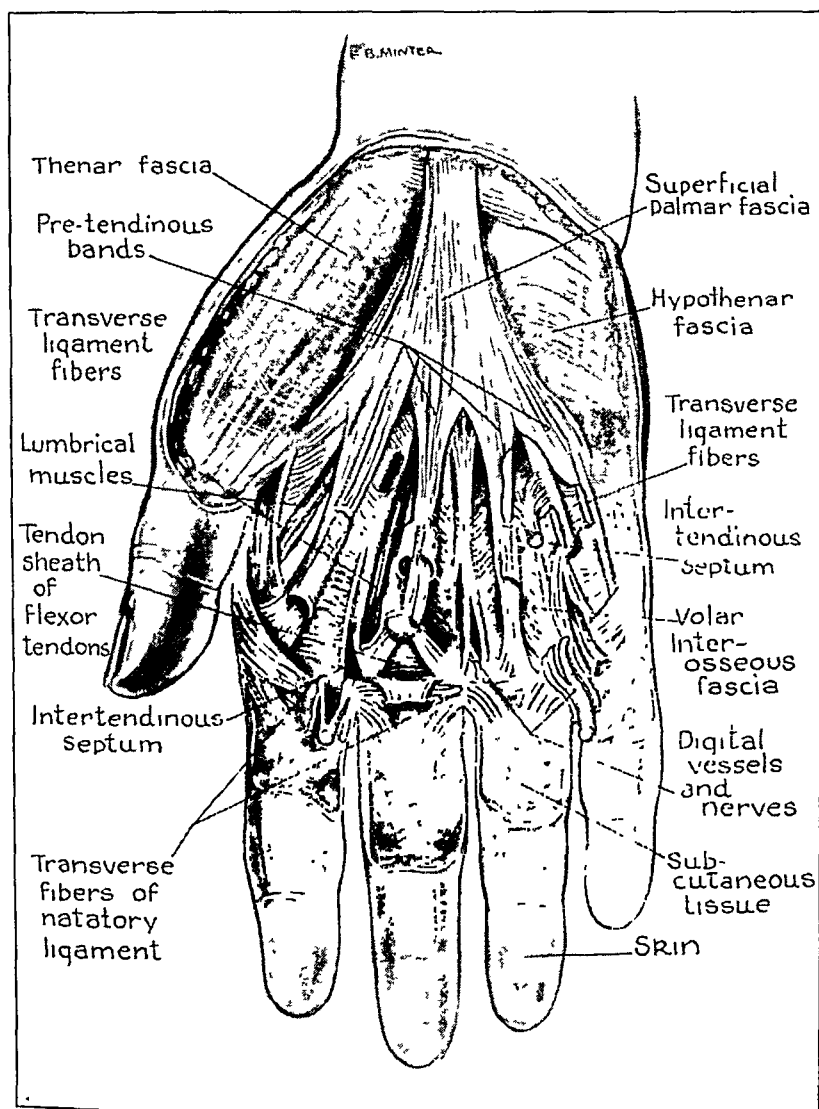


Fig. 1.—Drawing showing the gross anatomy of the palmar fascias and septums in the human hand. The superficial stratum merges, proximally, with the superficial fibers of the transverse carpal ligament; it extends laterally and medially as a thin sheath over the thenar and hypothenar muscle groups and divides distally into the pretendinous bands. The ring finger illustrates the distal longitudinal and transverse fibers of this layer as they terminate in the subcutaneous layer of the proximal portion of the finger. In the middle and index fingers, the pretendinous band and the transverse ligaments have been sectioned and reflected to demonstrate the deep fibers extending from the pretendinous band to the fibrous tendon sheath of the flexor tendons and the lateral extensions of this band into the base of the finger. The intertendinous septums and their attachments to the inter-osseous fascia and at the base of the fingers are also illustrated.

this deep fascial layer was continuous with the ligamentous structures on the volar surface of the wrist and the pronator quadratus muscle. Its transverse fibers became thickened opposite the metacarpal heads to form the transverse metacarpal ligament, and distally, it merged with the volar portion of the capsule of the metacarpophalangeal joint, the digital fibrous sheath of the flexor tendons and the periosteum of the proximal phalanges (fig. 1).

The three main vertical septums (intertendinous or paratendinous septums) were attached to the metacarpal bones and could be traced distalward to the digital fibrous tendon sheaths, to the capsule of the metacarpophalangeal joints and to the lateral aspects of the proximal phalanges (fig. 1).

In the available material it was not possible to demonstrate with satisfaction, even in cross sections of several whole hands, the vertical fibers described by Legueu and Juvara³ as extending from the pretendinous bands to the dorsum, between the metacarpal heads, becoming attached to the dorsal aponeurosis of the hand and forming sheaths for the interosseous muscles.

Comment.—The deformity in Dupuytren's contracture must depend, at least in part, on such factors as (1) the preexisting anatomic structure of the palmar fascia and (2) the extent of involvement not only of the superficial layer but also of all the related fascial layers and septums. Involvement of those fibers between the superficial fascial stratum and the skin leads to induration and puckering of the skin and to accentuation of the transverse palmar creases; this deformity, clinically, precedes finger deformities. The presence or the absence of pretendinous bands to certain fingers and the extent of their anatomic development, must predetermine, at least in part, which fingers will become deformed and the extent of this deformity. Flexion deformities, however, will be caused not only by involvement of these longitudinal bands—by virtue of their attachment to the skin and to the fibrous tendon sheaths—but also by the vertical septums and by the volar interosseous membrane, the fibers of which merge, distally, with the digital fibrous sheaths of the flexor tendons, the capsule of the metacarpophalangeal joints and the periosteum of the proximal phalanges. These flexion deformities of the fingers may become exaggerated by secondary shortening of the volar capsules of the metacarpophalangeal and the proximal interphalangeal joints and of their collateral ligaments and by adaptive shortening of the flexor tendons themselves.

The amount of operation (i. e., excision of the involved fascias) necessary to effect and maintain good correction of the deformities in

3. Legueu, F., and Juvara, E.: Des aponévroses de la paume de la main, Bull. Soc. anat. de Paris 67:383-400, 1892.

Dupuytren's contracture will depend also on these anatomic features. It has been the experience of most contemporary surgeons, as well as my own in the series herein reported, that treatment must consist of wide excision not only of the contracted superficial palmar fascia and its digitations but also of the attachments to the skin, the paratendinous septums and even the distal portions of the deep interosseous fascia. The correction of flexion deformities of the fingers may necessitate widespread excision and division of soft tissue and even resection of bone. Since this amount of operation has sometimes led to a functionally useless digit, the wisdom of immediate amputation of a severely deformed finger has become apparent.

MICROSCOPIC ANATOMY OF THE SUPERFICIAL PALMAR FASCIA IN
HUMAN HANDS PRESENTING NO GROSS ABNORMALITY
OF THIS STRUCTURE

Histologic preparations were made from both the palmar and the digital portions of the superficial palmar fascia from 27 cadaver specimens. Three of these specimens were from fetuses at the stage of 3, 6 and 9 months, respectively. The remaining 24 were obtained from 20 adult human cadavers whose ages varied between 16 and 85 years. Of these 20, 18 were male and 2 female; 13 were white, and 7 were Negroes. The distribution according to age groups was, more specifically, as follows: in the second decade, 1; in the third, 1; in the fourth 1; in the fifth, 1; in the sixth, 2; in the seventh, 8; in the eighth, 4; and in the ninth, 2.

The histologic structure of the superficial palmar fascia in all the specimens was found to be not unlike that of capsular and tendon tissues. A tendency to increasing thickness of the fascia and to greater density and compactness of the parallel collagenous fibers was apparent in the older age groups.

Although the palmar fascia was not distinguishable as a distinct layer in the hand of the 3 month fetus, it was evident in the hands of the 6 and the 9 month fetus. The features of the cellular structure of this layer in the latter 2 specimens were not distinctly different from those of the deeper muscle stratum.

In the adult specimens, the palmar fascia consisted of bundles of dense poorly cellular connective tissue, arranged longitudinally in some areas and transversely in others. The collagenous fibers were compacted into parallel bundles and demonstrated flattened and elongated nuclei and occasional small vascular channels. These features were demonstrable uniformly in all the specimens of the various age groups. It appeared, however, in the specimens representing the later decades of life that the fascial layer became thicker and more dense and the bundles of collagenous fibers more compacted. The resemblance of



Fig. 2—Photomicrographs showing: *A*, grossly normal palmar fascia ($\times 37$) from the left hand of the cadaver of a white man aged 22 years; *B*, grossly normal palmar fascia ($\times 37$) from the left hand of the cadaver of a Negro man aged 44 years; *C*, grossly normal palmar fascia ($\times 37$) from the right hand of the cadaver of a white man aged 62 years.

this fascia, especially in the older specimens, to tendon tissue was striking. The histologic features bore no definite relation to the sex or race of the subject or to the side of involvement (figs. 2 and 3).

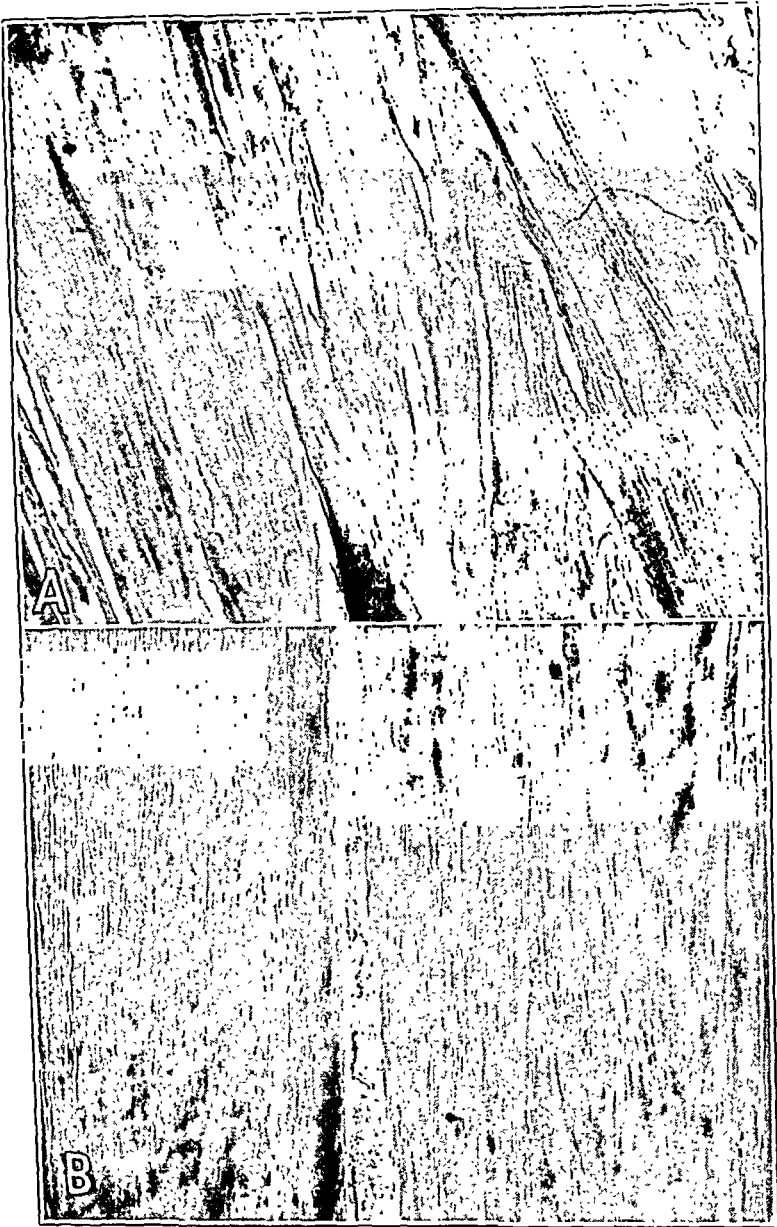


Fig. 3.—Photomicrographs showing: *A*, grossly normal palmar fascia ($\times 37$) from the left hand of the cadaver of a white man aged 70 years; *B*, grossly normal palmar fascia ($\times 37$) from the left hand of the cadaver of a white man aged 85 years. The fascial tissues shown in this and the preceding figure consist of bundles of parallel collagenous fibers with flattened elongated nuclei. In the older specimens, this tissue is less cellular and less vascular, while the collagenous fibers have lost their wavy character and become more closely compacted, thickened and hyalinized. This structure, especially in the older specimens, resembles that of tendon tissue.

Comment.—The histologic features of the palmar fascia in human fetuses and the histologic resemblance of this fascia to tendon tissue in adult human cadavers may be in keeping with the concept, defended by some anatomists, that the superficial palmar fascia represents the aponeurotic insertion of the palmaris longus muscle (when the latter is present). The theory, held by a few investigators, that this structure represents, in the human being, the tendinous counterpart of the atavistic muscle layer, the flexores breves manus superficialis, lacks sufficient supportive evidence.

The progressive thickening and condensation of the normal palmar fascia with advancing age may be of significance in the causation of Dupuytren's contracture, since this pathologic condition is most frequent in the later decades of life.

THE HISTOLOGY OF DUPUYTREN'S CONTRACTURE

The histology of Dupuytren's contracture has been extensively reviewed by Iklé,⁴ Davis and Finesilver,⁵ Ferrarini⁶ and Meyerding, Black and Broders.⁷ Most writers on this subject have recognized the essential process to be one of proliferation or hyperplasia of connective tissue, and they have noted the transition from the early features of a cellular tissue to the final stage of scarring. Some have interpreted this process as focal hypertrophy of connective tissue arising in the walls of the blood vessels. Others, without convincing evidence, have described the process as a chronic inflammatory one. Meyerding, Black and Broders⁷ stressed the importance of chronic inflammatory changes in the skin, the subcutaneous tissue and the interstitial connective tissue, in association with the more generally recognized fibroplastic process involving the palmar fascia, and these authors have suggested that the disease begins in the interstitial connective tissue and spreads to involve the other tissues of the palm. The resemblance of certain cellular areas in Dupuytren's contracture to fibrosarcoma is purely superficial, and the evidence is distinctly against the idea of a neoplasm.

In general, I conclude from my findings that the essential pathologic changes are those of active fibroplasia involving the palmar fibrous

4. Iklé, C.: Zur Histologie und Pathogenese der Dupuytren'schen Kontraktur, Deutsche Ztschr. f. Chir. **212**:106-118, 1928.

5. Davis, J. S., and Finesilver, E. M.: Dupuytren's Contraction, with a Note on the Incidence of the Contraction in Diabetes, Arch. Surg. **24**:933-989 (June) 1932.

6. Ferrarini, M.: Sulla anatomia pathologica e sulla etiopatogenesi della malattia del Dupuytren, Arch. ital. di chir. **57**:1-110, 1939.

7. Meyerding, H. W.; Black, J. R., and Broders, A. C.: The Etiology and Pathology of Dupuytren's Contracture, Surg., Gynec. & Obst. **72**:582-590. 1941.

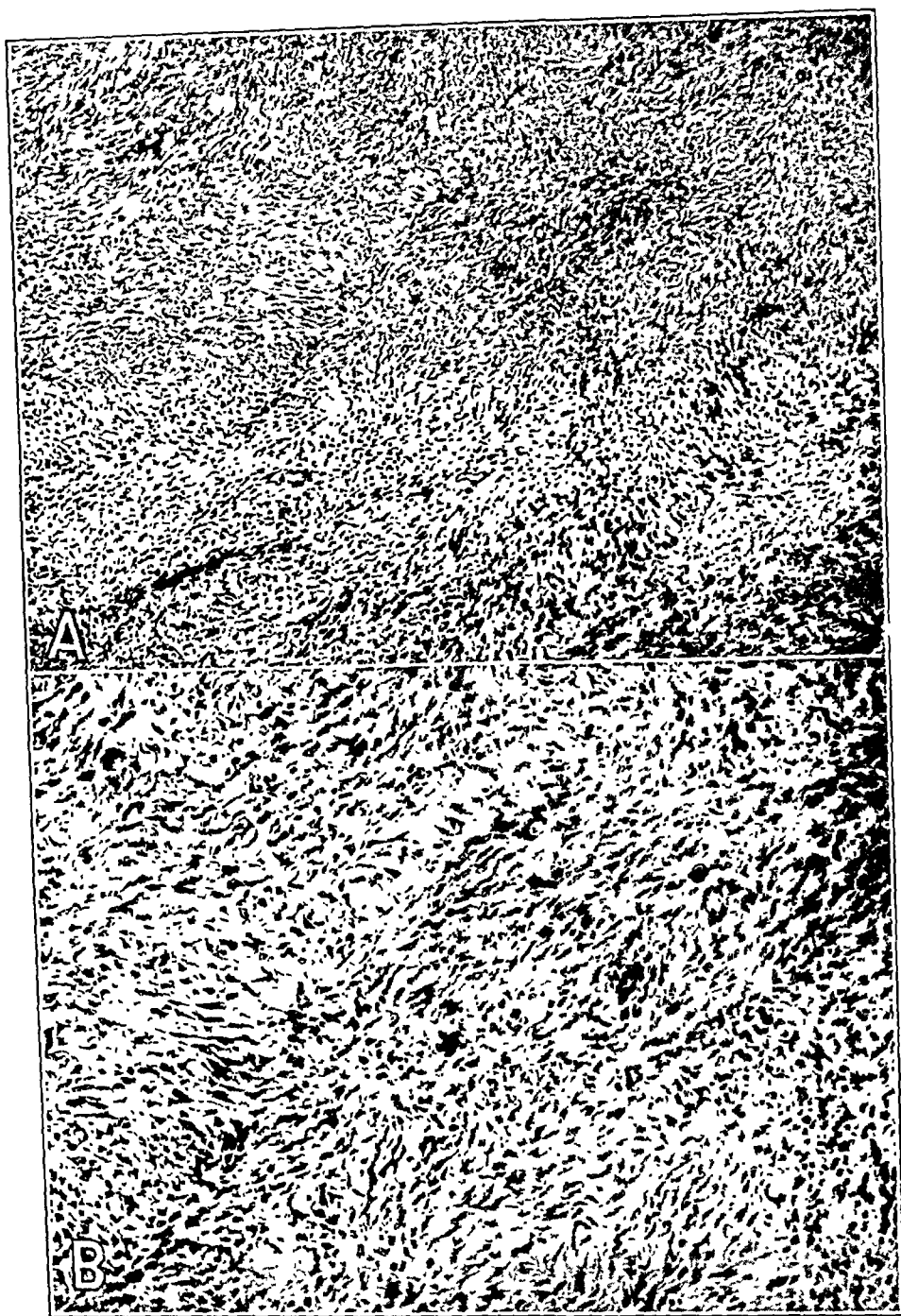


Fig. 4.—Photomicrographs showing: *A*, tissue ($\times 47$) from the left hand of a 46 year old plasterer with Dupuytren's contracture of approximately ten years' duration. The tissue is hypercellular, and, especially in some areas, the nuclei are densely compacted, and there is little or no intercellular matrix. *B*, a section ($\times 94$) from the center of the area illustrated in *A*. The nuclei are round, oval or elongated, stain deeply, and in some areas are closely compacted and form occasional multinucleated structures. The intercellular matrix is increased in the less cellular areas.

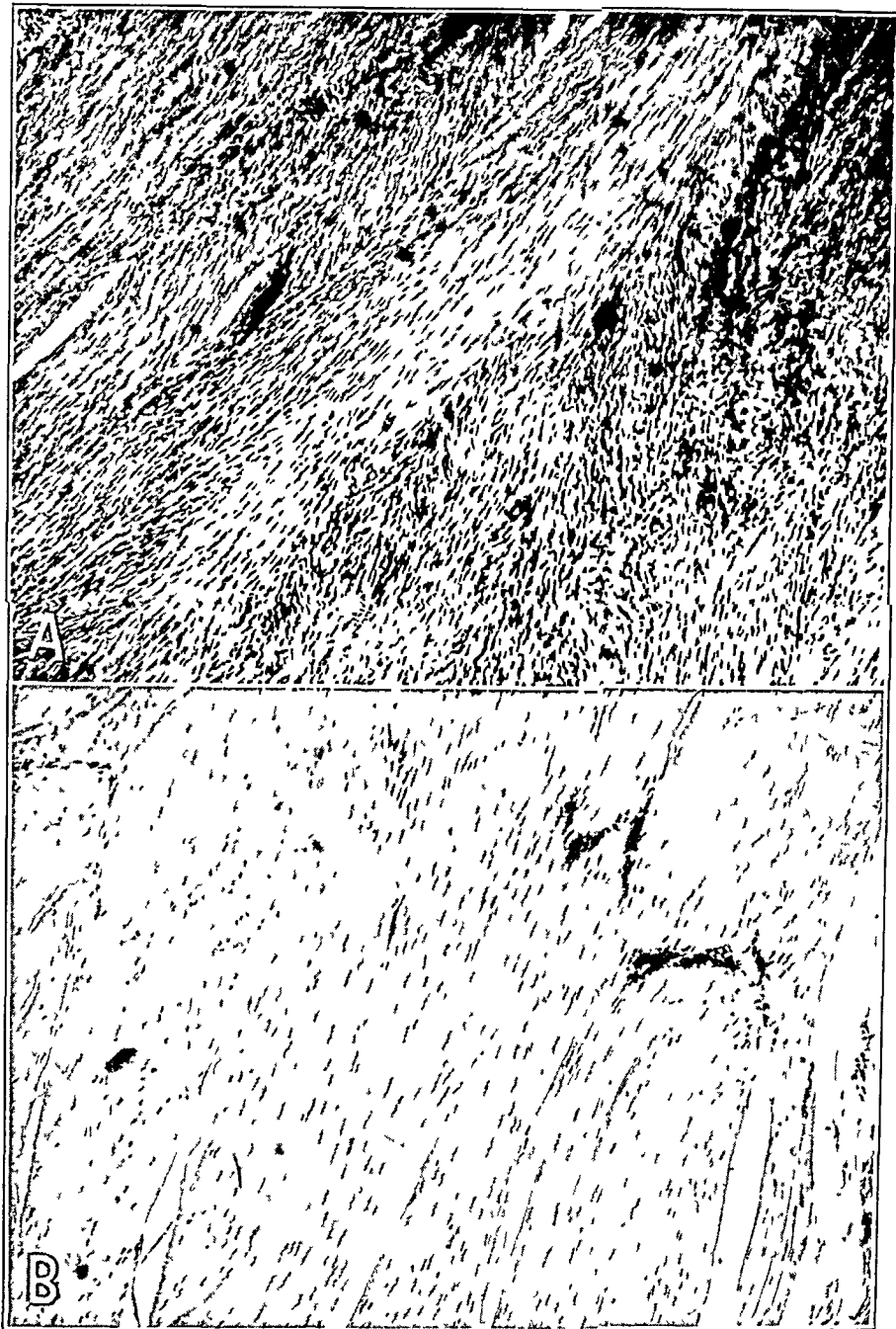


Fig 5—Photomicrographs showing. *A*, another area ($\times 47$) in the same histologic preparation as that shown in figure 4. The tissue structure varies from that of hypercellular regions of irregular structure through less cellular areas with more intercellular matrix and a tendency for the parallel arrangement of fibroblasts to poorly cellular areas in which the intercellular tissue predominates and in which the nuclei are much flattened and elongated. *B*, another area ($\times 47$) from the same histologic preparation as that shown in figure 4. In this region the parallel collagenous fibers are densely compacted and hyalinized, and the nuclei are sparse, flattened and elongated, so that the structure is identical with that of tendon tissue

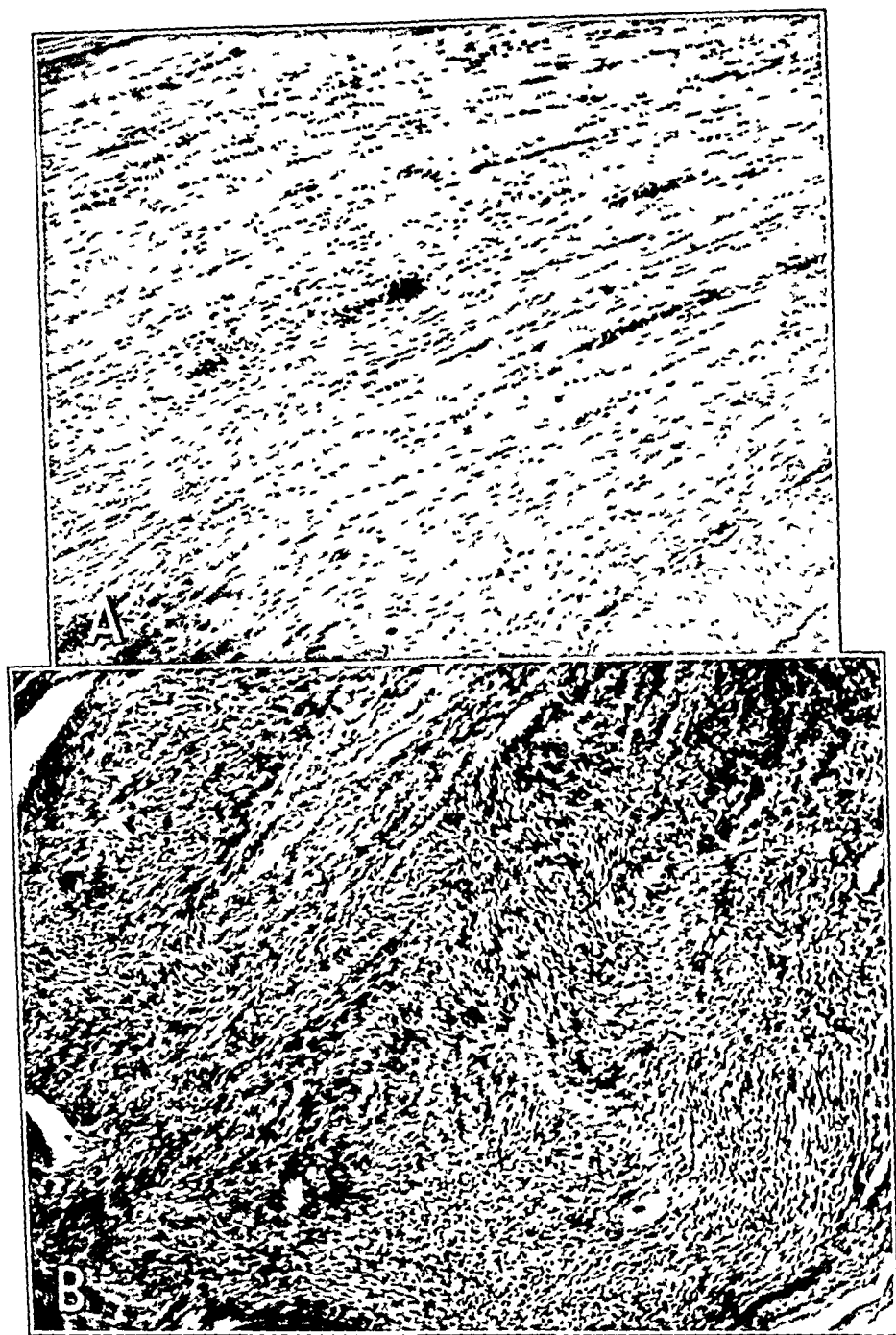


Fig. 6.—Photomicrographs showing: *A*, tissue ($\times 50$) from the right hand of a 47 year old painter with Dupuytren's contracture of approximately three months' duration. The connective tissue is densely compacted and poor in cells and resembles capsular or tendon tissue. *B*, tissue ($\times 44$) from the left hand of a 53 year old watchman with Dupuytren's contracture. The deformity had been present for approximately twenty years. The tissue is hypercellular and shows closely compacted round and oval nuclei and little intercellular matrix. Although there is active fibroplasia, there are no mitotic figures, and the lobule of tissue illustrated is clearly delimited by a zone of dense fibrous tissue. That the histologic activity bears no definite relation to such clinical features as the duration of the pathologic process is demonstrated in cases such as these.



Figure 7

(See legend on opposite page)

tissues, of which the palmar aponeurosis is the chief constituent. Associated changes were present also in the skin and the subcutaneous tissues and involved the vessels and the tendon sheaths. This proliferative process was interpreted as benign local fibroplasia which terminated in the final picture of avascular scarring. Inflammatory features were not constant. The cellular proliferation was uniform and orderly, and there was no evidence of invasiveness. No definite correlation between the clinical and the histologic features of Dupuytren's contracture could be ascertained.

The clinical features in this series of 35 cases were identical with those reported by previous authors. The age distribution was as follows: 30 to 39 years, 3 cases; 40 to 49, 12; 50 to 59, 14; 60 to 69, 6. The youngest patient was 30 years of age and had had the deformity for about four years; the oldest was 68 and had had the deformity for about four months. Thirty-three of the patients were male, and 2 were female. In only 18 of the 35 cases was the patient engaged in an occupation in which the involved hand might have been subjected to repeated trauma. The disorder was bilateral in 19 cases (more advanced on the right in 8; more advanced on the left in 6; equal in 5) and unilateral in 16 (in the right hand in 12; in the left hand in 4). The deformity present consisted only of thickening of the palm in 4 of the 54 hands, while palmar deformity was associated with deformity of one or more fingers in the remaining 50 hands—the fourth or fifth fingers or both being involved in all of these hands; the third in 7; the second in 1, and the thumb in 1. The history of the duration of the deformities prior to treatment varied from a minimum of three months to a maximum of twenty years. There was associated gout in 1 case, diabetes mellitus in 1 case and polyarthritis in 2 cases. In the remaining cases, all clinical and laboratory findings were normal.

The patient usually stated that he or she had noted a small nodule or induration followed by puckering of the palmar skin—most often

EXPLANATION OF FIGURE 7

Photomicrographs showing: *A*, tissue ($\times 50$) from the left hand of a 55 year old barber with Dupuytren's contracture. The contracture was of approximately seven years' standing. The fibrous tissue is uniformly dense but moderately cellular. Large aggregates of lymphocytes, usually arranged about the periphery of blood vessels, constitute a prominent feature. *B*, tissue ($\times 50$) from the right hand of a 36 year old clerk with Dupuytren's contracture. The contracture had been noted for only three months. The histologic features in this section are identical with those of *A*. That these areas of perivascular lymphocytic infiltration, when present, bear no definite relation to such clinical features as age of the subject and duration of the pathologic process or to other more constant histologic features is demonstrated in cases such as these.

at the base of the fourth and fifth fingers—which was followed months or years later by the development of flexion contracture of the affected finger, associated with the appearance of a thickened band extending from the concavity of the palm to as far as the proximal interphalangeal joint of the involved finger. Later, implication of adjacent fingers was noted together with the appearance of more nodules and funnel-like depressions of the palm, further induration and creasing of the skin and atrophy of the subcutaneous tissues. In only 2 cases was there a history of brief tenderness of the involved palm and finger.



Fig. 8.—Photomicrograph showing tissue ($\times 47$) from the right hand of a 30 year old truck driver with Dupuytren's contracture of approximately four years' duration. The deformity recurred six months after incomplete excision. The tissue illustrated was obtained at the first operation. In the main, it is composed of compacted and hyalinized fibers in which the nuclei are flattened and elongated. About some of the blood vessels there are collections of cells which are not inflammatory but which represent localized areas of hypercellularity in the perivascular connective tissues. As demonstrated in this case and in others, the incidence of recurrence appears to bear no definite relation to the histologic activity of the involved tissues.

In all 35 cases, the involved fascias were subjected to surgical excision. Recurrence took place in 6 cases—after obviously incomplete operation in 3 and after extensive and apparently complete operations in the other 3.

As to the microscopic findings, specimens in which portions of the skin overlying the contracted fascia were available showed widespread involvement of the skin and subcutaneous tissue in addition to the changes in the aponeurosis. The epidermis was hypertrophied and keratinized and the corium intensely affected by fibrosis, while the papillae had disappeared. There were scattered collections of lymphocytes concentrated especially within and just beneath the corium. The subcutaneous adipose tissue was diminished or almost absent and contained scattered blood vessels and sweat glands.

In the deeper layers there were large collections of cellular tissue with little or no stroma. The closely compacted nuclei in these hyper-



Fig. 9.—Photomicrograph showing a section ($\times 50$) of a painful nodule removed from the plantar fascia of the right foot of a 48 year old woman. There were several such nodules in the plantar fascia of both feet, but the palmar fascias were apparently uninvolved. This area represents cellular noninflammatory connective tissue hyperplasia. The histologic structure is similar to the fibroplasia occurring with Dupuytren's contracture (compare with fig. 4 *A*). In other regions (not shown) the connective tissue was more mature and had undergone hyalinization in places.

cellular areas were round or oval and stained deeply. Rarely, a mitotic figure was noted. Such areas were interpreted as representing actively proliferating tissue. They tended to be arranged in lobules, the tissue increasing in maturity from the center to the periphery, and these lobules were delimited from the surrounding tissues by a zone of fibrous poorly cellular connective tissue (figs. 4 and 6 *B*). In other regions, the connective tissue cellularity was less marked, and there

was a greater amount of intercellular matrix. The nuclei in such areas were spindle shaped or elongated and flattened, and the cells tended to be arranged in parallel masses (fig. 5). In still other areas, the collagen fibers were hyalinized and closely compacted, and the nuclei were considerably thinned and elongated. This fibrosis and scarring progressed even to the extent of producing resemblance to tendinous tissue (figs. 5 *B* and 6 *A*).

In most instances, these variations in connective tissue cellularity were recognizable within the same specimen (figs. 4 and 5). The

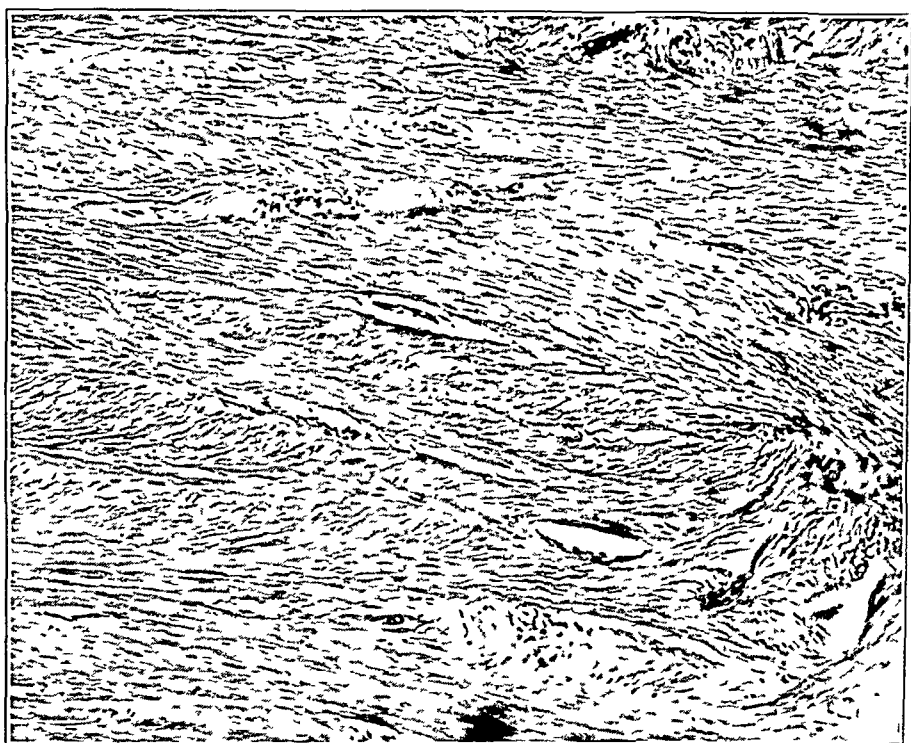


Fig 10—Photomicrograph showing a section ($\times 50$) from a keloid of the left ear of a 36 year old Negro woman, which had arisen after piercing of the lobule ten years previously. The tissue is densely fibrous; the collagenous fibers are arranged in parallel bundles with flattened nuclei and few blood vessels. Scattered collections of lymphocytes are evident about the periphery of some of the vessels. The structure is tendon-like and closely resembles the more mature areas in cases of Dupuytren's contracture.

growth was uniform and orderly, and there was no indication of invasiveness. In some regions, especially between the lobules of cellular tissue, the connective tissue was loose and relatively vascular. In such areas in some of the specimens, collections of lymphocytes were

demonstrable, but this feature was inconstant. These collections, when present, were usually but not always perivascular in arrangement (fig. 7).

Similar connective tissue hyperplasia was observed in the plantar fascia of a subject in whom there was no demonstrable palmar involvement (fig. 9). Although there was no record of clinical involvement of the plantar fascias in the 35 cases of Dupuytren's contracture in this study, it should be borne in mind that the generous subcutaneous adipose tissue and thick skin of the sole of the foot might interfere



Fig. 11.—Photomicrograph showing a section ($\times 50$) from a hypertrophied scar of the hand, following on a burn one year previously, in a 5 year old white boy. The connective tissue was dense and poorly cellular and showed a pronounced tendency toward whorl formation. Some of the vessels revealed scattered lymphocytes about their periphery—a feature which was prominent in less densely fibrous regions of this specimen.

with the detection of early or even moderate involvement of this fascia, a structure anatomically identical with palmar fascia.

Remarks.—The following conclusions were drawn:

1. The pathologic tissues in this series of 35 cases could not be grouped or graded on the basis of predominance of any distinctive feature or features. In most of the material, wide variation in histologic characteristics was evident within the same specimen.

2. The variable cellularity of the tissues did not appear to indicate accurately the activity of the proliferative process. No constant relation could be ascertained between the histologic picture and such clinical features as the age of the patient, the duration of the pathologic process (as noted by the patient) and the severity and extent of the deformity (figs. 6 and 7).

3. No definite relation could be established between the histologic picture and the likelihood of recurrence, for in the cases in which there was recurrence, the pathologic features were not different from those in cases in which no recurrence was clinically demonstrable (fig. 8).



Fig. 12.—Photomicrograph showing a section ($\times 45$) from a desmoid excised from the wall of the abdomen of a 31 year old woman. The desmoid had appeared at the site of the healed scar of an uncomplicated laparotomy, performed four years previously. In some areas, the tumor is composed of closely compacted poorly cellular connective tissue, while in other regions the tissue is more cellular, well vascularized and loose in texture.

4. The evidence in favor of a chronic inflammatory basis for palmar fibrosis was not striking. The presence of collections of lymphocytic cells was observed in only 13 of the 35 specimens; in some instances their distribution was widespread, while in others it was sparse. When present, these collections bore no definite relation to the clinical features or to other histologic features (fig. 7). Even in those cases in

which tenderness of the thickened palmar fascia and of the involved fingers had been present clinically, inflammatory features were not clearcut. These collections of inflammatory cells had to be carefully differentiated from focal collections of compacted hypercellular tissue immediately adjacent to some of the blood vessels. The significance of these lymphocytic collections is not clear, but it is noteworthy that they were abundantly demonstrable in cases in which there was keloid formation—another example of localized benign fibroplasia (figs. 10 and 11).

5. There was no evidence to substantiate the idea that the proliferative process involving the palmar fascia might originate from the walls of the blood vessels. In some instances, thickening of the vessel wall was noted, and this was interpreted as possibly representing concomitant fibroplasia in the vascular connective tissues or, in the older specimens, a senile degenerative process.

6. In those areas in which fibroblasts were abundant, interlaced and had assumed whorl-like arrangements, the histologic structure was not dissimilar to that of keloid, fascial desmoid and fibroma (figs. 10, 11 and 12).

7. Identical connective tissue hyperplasia may involve plantar fascia (fig. 9).

COMMENT

Most of the theories relating to the causation of Dupuytren's contracture appear to have been founded on wholly inadequate evidence. The importance of such factors as trauma, chronic specific or non-specific inflammatory processes, circulatory stasis, toxins (focal infections, gout, diabetes mellitus, arthritis), embryologic malformations, peripheral or central neurologic disturbances and endocrinopathies has not been substantiated by a critical analysis of the clinical and histologic material in this investigation and of the data reported by other writers.

Certain other factors, however, do appear to have some significance:

Heredity.—The occurrence of Dupuytren's contracture in several generations in the same family and the high familial incidence in large series of cases have been noted by numerous authors.

Senility.—The contracture occurs most frequently in middle life and in old age. It is not unlikely that this fact may be related, at least in part, to the presence of such degenerative and proliferative processes as were noted in this study in the vascular and connective tissues of normal palmar fascias in patients in the later decades of life.

Fibroblastic Diathesis or Predisposition.—The theory of a constitutional predisposition to connective tissue proliferation has been suggested by some observers because of the concomitant occurrence in some cases

of Dupuytren's contracture of thickening and contracture of the plantar fascias and of induration of the penis. There is a striking histologic resemblance of the fibroblastic process in Dupuytren's contracture to other localized fibroplasias, such as keloid and fascial desmoid. A keloid is a localized overgrowth of hyaline connective tissue developing in the skin of a predisposed person, usually at the site of scarring, although it may arise spontaneously. A desmoid is a fibroma of the abdominal wall. Although the relation of desmoids to trauma (e. g., from gestation) cannot be overlooked, the congenital origin of some and the origin of many others in the scars of uncomplicated laparotomy suggest an anatomic predisposition of the affected tissue to desmoid formation in certain subjects. Furthermore, like Dupuytren's contracture, both keloid and fascial desmoid are prone to recur despite extensive surgical excision.

SUMMARY AND CONCLUSIONS

This study of Dupuytren's contracture embraces: (1) the normal gross anatomy of the human palmar fascia (material: 60 hands); (2) the microscopic anatomy of the palmar fascia in human cadavers presenting no gross abnormality of this structure (material: 27 specimens); (3) the histologic features of Dupuytren's contracture (material: 35 cases).

The deformity in Dupuytren's contracture was found to be intimately related to the gross anatomic structure of the fascial layers and septums of the hand. Widespread surgical excision of these tissues is essential to effect and maintain correction of the deformity.

The tendon-like structure of normal palmar fascia and the proliferative and degenerative changes which occur in this tissue with advancing years may have some bearing on the development of fibrosis of the palmar tissues in Dupuytren's contracture—a condition most prevalent in the later decades of life.

The essential process in Dupuytren's contracture is benign fibroplasia of the palmar connective tissues. Inflammatory features are not constant, nor is there evidence that the proliferative process arises from the walls of blood vessels. The histologic features and the clinical behavior of this fibroblastic process bear a striking resemblance to those of other localized fibroplasias, such as keloid and fascial desmoid.

Such factors as heredity, senility and fibroblastic diathesis or predisposition appear to be of importance in the causation of Dupuytren's contracture.

REFLEX CHANGES IN RESPIRATION INDUCED BY DISTENTION OF THE SMALL INTESTINE

ROBERT T. CROWLEY, M.D.

DETROIT

The importance of distention in the various portions of the gastrointestinal tract has been frequently stressed in experimental and clinical literature. Such interest has arisen largely from repeated demonstrations that the distention inevitably appearing on intestinal obstruction is the factor chiefly responsible for the grave physiologic disturbances associated with that condition.¹ Whether experimentally produced or resulting from actual pathologic conditions, excessive intraluminal pressure in the small intestine has been shown to produce a variety of local and general effects. Among the changes induced locally in the distended bowel segment are alterations in the motility,² the circulation,³ the absorption⁴ and the secretion.⁵ Changes of a more general character occurring in the entire volume of circulating blood include disturbance of the cell-plasma ratio⁶ and fluctuation of the level of nitrogenous substances in the blood.⁷ Certain other effects, apparently reflex responses to the stimulus of distention, are much less familiar. Among these is the marked respiratory response elicited by the stimulus of excessive dis-

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From the Department of Surgery, Wayne University College of Medicine.

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6. Fine, J.; Fuchs, F., and Gendel, S.: Changes in Plasma Volume Due to Decompression of the Distended Small Intestine, *Arch. Surg.* **40**:710 (April) 1940.

7. Haden, R. L., and Orr, T. G.: Excretion of Nitrogen After Upper Gastrointestinal Tract Obstruction, *J. Exper. Med.* **45**:433, 1927.

tention rapidly induced in the small intestine. A search of the literature has revealed little dealing with this phenomenon. It is the purpose of this communication to present observations obtained in an experimental investigation of this particular effect, namely, the changes produced in the character and the volume of respiration by excessive distention rapidly induced in the small intestine.

PROCEDURES

Dogs were the experimental animals employed; 30 were used in the course of the experiments. With the animal under anesthesia produced by intravenous and intraperitoneal injections of soluble pentobarbital (30 mg. per kilogram of body weight), a cannula was placed in the right carotid artery and a pleural cannula inserted in the chest. The blood pressure was recorded on a kymograph with a

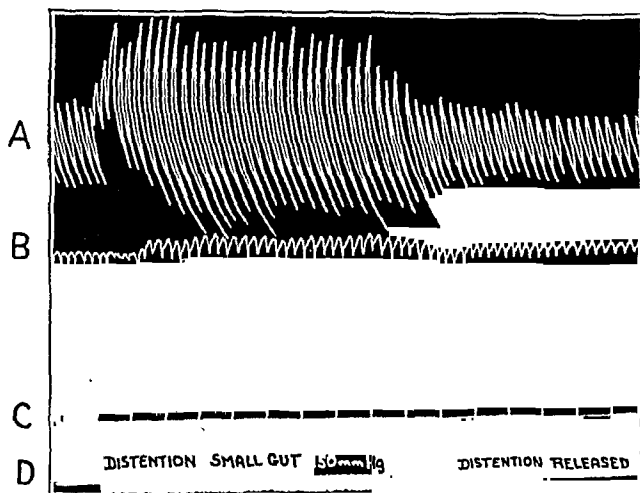


Fig. 1.—Typical alterations in the respiration and the blood pressure obtained on distention of a segment of the ileum 2 feet (61 cm.) from the ileocecal valve. The dog weighed 12.5 Kg. Anesthesia was induced by the intravenous injection of 30 mg. per kilogram of body weight of soluble pentobarbital. *A*, respiration; *B*, blood pressure; *C*, time units at intervals of six seconds and at a blood pressure level of zero; *D*, signal.

mercury manometer, and the respiratory tracing was obtained simultaneously by means of a tambour. The abdomen was opened through a midline incision, and the distending tube, fashioned from a Foley catheter, was inserted into the lumen of the intestine through an incision in the bowel wall at the antimesenteric border perpendicular to the long axis. To prevent possible slipping of the tube from its position in the lumen, two sutures were passed through the tube and the entire thickness of the intestine; thus it was secured firmly in place. Distention of the intestine was performed at intervals by injecting varying quantities of air from a 50 cc. syringe into the inflation cuff of the catheter lying in the lumen. The intraluminal pressure was measured by means of a mercury manometer interposed between the distending tube and the syringe used for the injection of air.

Numerous readings during control periods without distention were taken for all animals. Distention of the tube was carried out with the segment of the bowel outside the abdominal cavity covered with cloths moistened with warm 0.9 per cent solution of sodium chloride. Various procedures were then undertaken to learn the effect which they might produce on the respiratory changes elicited by distention. These procedures included unilateral and bilateral vagotomy, bilateral adrenalectomy, section of the spinal cord at the level of the second thoracic vertebra,

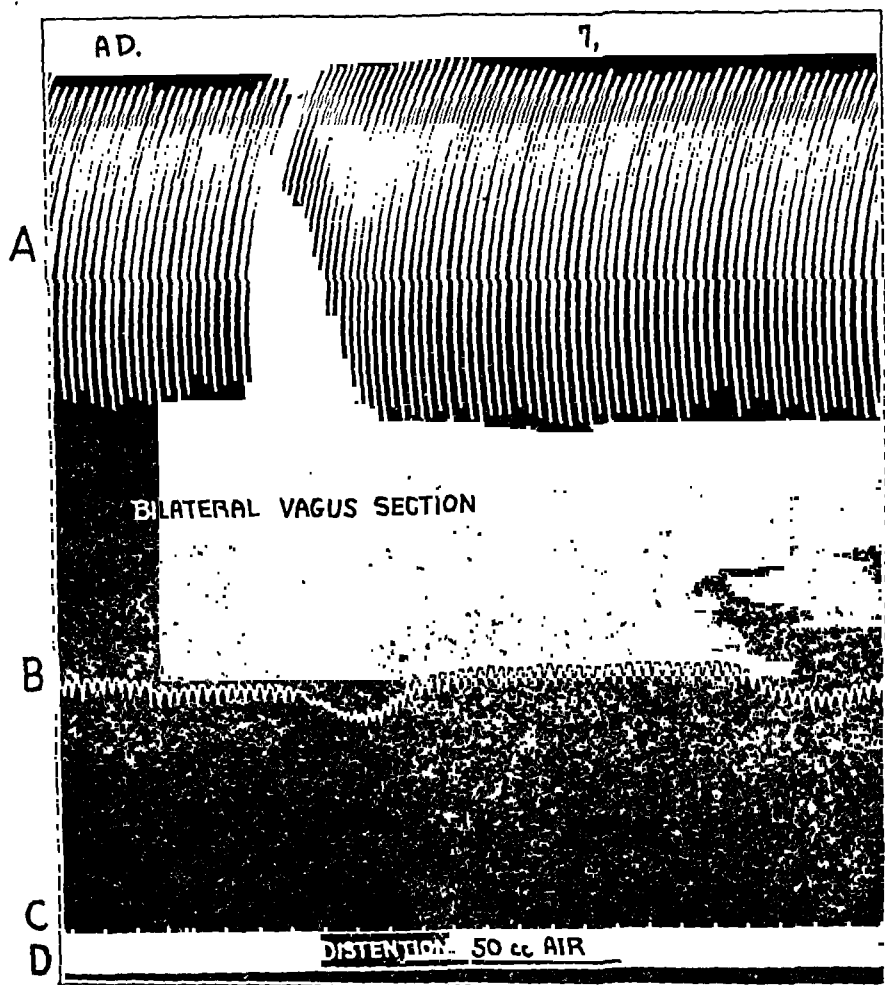


Fig. 2.—Persistence of the respiratory and the blood pressure changes occurring on distention of an isolated loop of the jejunum with an intact mesentery after previous bilateral adrenalectomy and bilateral vagotomy. The dog weighed 17 Kg. Anesthesia was induced by the intravenous injection of 30 mg. per kilogram of body weight of soluble pentobarbital.

section of the splanchnic nerves to the bowel segment, cocaineization of the splanchnic nerves to the bowel segment and the intravenous administration of atropine sulfate (6 mg. per kilogram of body weight) and of ethyl yohimbine (5 mg. per kilogram of body weight). The effect of employing the faradic current to stimulate the splanchnic nerves of the undistended segment of the intestine, in which the dis-

tending tube was placed, also was observed. To elucidate more clearly the effect of the distention stimulus on respiration before and after the procedures just described, the observations made will be detailed in conjunction with typical kymographic tracings in each instance.

OBSERVATIONS

1. Distention of various segments of the small intestine from the duodenum to the ileocecal valve invariably produced a marked respiratory

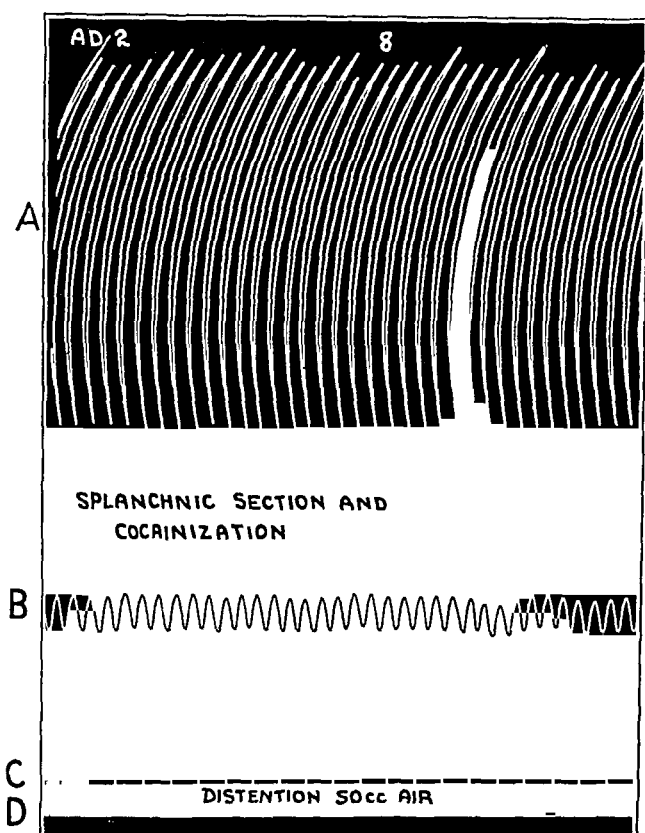


Fig. 3.—Disappearance of the respiratory effects elicited by distention of a loop of the ileum after section and cocaine of the splanchnic nerve fibers to the distended bowel segment. The dog weighed 18.5 Kg. Anesthesia was induced by the intravenous injection of 30 mg. per kilogram of body weight of soluble pentobarbital.

change. This change consisted of an arrest in the respiratory rhythm, usually in the expiratory phase, sometimes of apnea, for a period, followed immediately by an increased respiratory volume, which persisted as long as the distention of the intestine was maintained. On release of the distention, respiration promptly returned to the previous normal

state. Coincident with the change observed in respiration on distention of the intestine, there was invariably marked fluctuation of the blood pressure. This consisted of an initial drop in the pulse pressure, usually accompanied by a fall of the blood pressure level, immediately succeeded by a marked elevation of the pressure level, which was maintained as long as the bowel remained distended; on deflation the blood pressure returned to approximately the normal level (fig. 1). Both the respiratory

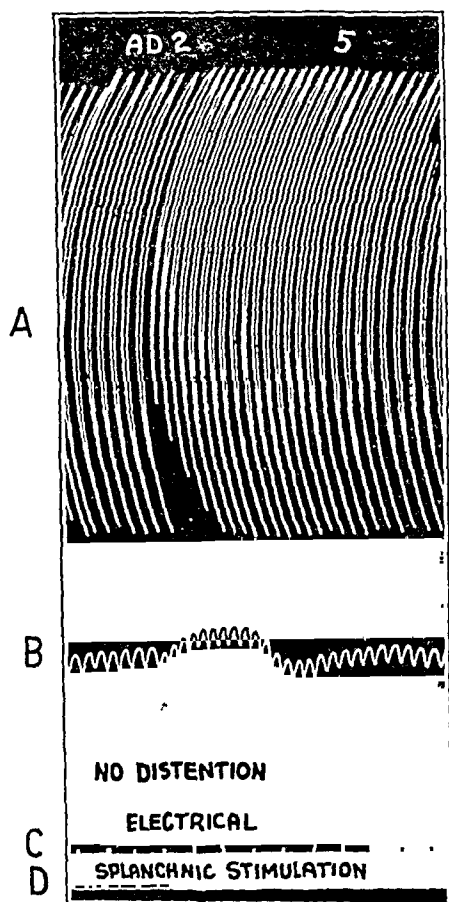


Fig. 4.—Similarity between the respiratory and the blood pressure effects obtained by electric stimulation of the splanchnic nerve fibers in the undistended bowel segment and those elicited by distention. The dog weighed 18.5 Kg. Anesthesia was induced by the intravenous administration of 30 mg. per kilogram of body weight of soluble pentobarbital.

and the blood pressure effects were roughly in direct proportion to the amount of distention induced—the greater the distention, the more accentuated the respiratory and circulatory changes. Likewise, both the respiratory and the blood pressure changes attending distention varied

inversely with the depth of the narcosis; they were appreciably less when a greater dose of the anesthetic drug was administered, although they never disappeared entirely.

2. Unilateral and bilateral section of the vagi in the neck were performed before distention and exerted no effect on the characteristic changes occurring on subsequent distention of the bowel segment (fig. 2).

3. Bilateral adrenalectomy performed on animals one hour before distention failed to show any influence whatever on the respiratory and the blood pressure changes elicited by subsequent periods of distention (fig. 2).

4. When the segment of the intestine to be distended was entirely separated from the rest of the bowel with its mesenteric connections left intact (formation of an isolated loop), distention in that segment

Experiments with Respect to the Effect of Distention of the Small Intestine

Procedure	Dogs	Result
Distention only.. . . .	30	Marked respiratory and blood pressure changes
Distention after vagotomy	12	Marked respiratory and blood pressure changes
Distention after adrenalectomy.. . . .	2	Marked respiratory and blood pressure changes
Distention in an isolated loop of the intestine	6	Marked respiratory and blood pressure changes
Distention after the administration of atropine sulfate	6	Marked respiratory and blood pressure changes
Distention after the administration of ethyl yohimbine	2	Marked respiratory and blood pressure changes
Distention after section of the spinal cord	4	No effect on respiration or blood pressure
Distention after section and cocaine-zation of the splanchnic radicals	2	No effect on respiration or blood pressure
Faradic stimulation of the splanchnic radicals	2	Marked respiratory and blood pressure changes, similar to, if not identical with, those obtained by distention

produced the same characteristic changes in respiration and blood pressure as before (fig. 2).

5. The intravenous administration of either atropine sulfate (6 mg. per kilogram of body weight) and/or ethyl yohimbine (5 mg. per kilogram of body weight) exerted no influence on the effect produced by the distention stimulus after intervals of one-half, one and two hours.

6. Section of the spinal cord at the level of the second thoracic vertebra in animals previously prepared completely eliminated both the respiratory and the blood pressure changes produced by distention.

7. The respiratory and the blood pressure effects also were entirely absent when distention was produced after isolation and transection of the splanchnic nerve radicals to the bowel segment in which the distending tube was placed. Cocainization of these splanchnic radicals with 2 per cent solution of cocaine produced the same effect as section of the fibers (fig. 3). The use of the faradic current to stimulate the intact fibers of the splanchnic radicals to the undistended segment produced

changes in the respiration and the blood pressure strikingly similar, if not identical, with those obtained with the stimulus of distention (fig. 4).

With regard to the preceding observations, it should be stated that the results obtained under the conditions described were the same in all employed for confirmation. The table briefly summarizes these observations.

COMMENT

These observations indicate that the variation in the respiration and the blood pressure observed after distention of the various parts of the small intestine are a definite physiologic response to the distention stimulus. That this phenomenon is of a reflex character cannot be doubted. It is well known that mechanical stimulation of the viscera produces marked reflex changes in the respiration and the blood pressure of completely anesthetized animals. Attention has been drawn also to the fact that the specific stimulus of distention is capable of producing marked respiratory and blood pressure changes when applied to such hollow viscera as the gallbladder and the rectum. The reflex respiratory changes elicited by distention of the small intestine have apparently received but little consideration. In 1928, Schrager and associates⁸ showed that excessive distention of the biliary passageways greatly influenced the character of the respirations in experimental animals. In this work clinical examples also were set forth to show that the changes produced by distention of the biliary passages were sufficiently marked to be used as a diagnostic criterion. Moreover, these investigators also noted that distention of the stomach and the jejunum produced some inhibition of respiration which was followed by an increase, although not as marked as that appearing on distention of the biliary passages.

Postulating that the same responses are elicited by distention of the small intestine of the human subject as have been demonstrated in the dog, it does not seem unreasonable to assume that respiration may be considerably modified by the presence of conditions in which excessive distention of the small intestine occurs.

Whatever clinical significance may be attached to the respiratory and the blood pressure changes associated with distention of the small intestine, the present observations are primarily concerned with their physiologic aspects. From these observations it appears that the phenomenon is entirely consistent in its appearance although individual quantitative variations do occur. It is not apparently a specific reaction to the distention stimulus alone, since stimulation of the splanchnic radicals to the undistended bowel segment by other means (faradic current) elicits a similar response. It also appears that the afferent

8. Schrager, V. S., and Ivy, A. C.: Symptoms Produced by Distention of the Gallbladder and Biliary Ducts, *Surg., Gynec. & Obst.* **47**:1, 1928.

impulses set up by the distention stimulus travel by way of the visceral afferent fibers in the splanchnic radicals to the distended bowel segment and not by way of the vagal ramifications, since the respiratory and the blood pressure effects persist unaltered after vagal section and disappear when the splanchnic radicals are cut or cocainized. That these visceral afferent fibers run more or less directly from the bowel into the mesentery and do not pass for any length in the bowel wall before entering the mesentery is demonstrated by the persistence of the effect on respiration in isolated loops. It is interesting to note in this connection that distention of a portion of the intestine about 2 inches (5 cm.) in length will produce the effect. It is obvious that some part of the nervous pathway, either afferent or efferent, producing the effect lies in the spinal cord from the fact that section of that structure at the level of the first or the second thoracic vertebra completely abolishes the respiratory changes. The fact that atropine sulfate and ethyl yohimbine in doses sufficient to remove parasympathetic and sympathetic action do not eliminate the respiratory changes occurring on distention indicates that the anatomic efferents, both cholinergic and adrenergic, are only slightly if at all involved.

SUMMARY

Marked respiratory changes, reflex in character, invariably follow excessive distention rapidly induced at any level of the small intestine of the anesthetized dog. These changes are of a characteristic pattern and are accompanied by synchronous fluctuations in the blood pressure. They are apparently initiated by afferent impulses arising from the stimulus of distention and mediated by fibers of the splanchnic nerve radicals to the distended bowel segment and subsequently by pathways in the spinal cord, since they are eliminated by complete section of either of these structures.

The vagus nerves and the adrenal glands are not involved in the production of the respiratory and the blood pressure effects since these continue to appear after transection of the former and total extirpation of the latter.

Drugs inhibiting the action of the efferent components of the autonomic nervous system, both adrenergic and cholinergic, exert little or no action on the respiratory alteration appearing on distention. Drugs depressing the visceral afferent impulses from the distended bowel segment lessen the respiratory and blood pressure phenomena and, if given in sufficient doses, abolish them entirely.

Drs. Charles G. Johnston and Frederick Yonkman gave assistance and advice throughout the experiment.

CARCINOMA OF THE FEMALE BREAST

AN ANALYSIS OF THE END RESULTS AFTER FIVE YEARS IN ONE
HUNDRED AND NINETY-TWO CASES, WITH SPECIAL CONSIDERATION
OF PREOPERATIVE IRRADIATION

L. CLARENCE COHN, M.D.

BALTIMORE

In an earlier article¹ I published the data on 192 cases of primary and recurrent carcinoma of the female breast occurring during the period from Jan. 1, 1931 to Dec. 31, 1935. Patients observed during this time were selected for study because this period marked the beginning of my experience with preoperative irradiation for operable carcinoma of the breast. In table 1 (reproduced from my earlier article) the classification of patients according to method of treatment

TABLE 1.—*Classification of Patients According to Treatment and Results*

Group	Status	No. of Patients
1	Preoperative irradiation and complete operation.....	43
2	Complete operation; no preoperative irradiation.....	51
3	Irradiation only, including excision of tumor and biopsy.....	42
4	Excision of breast only.....	9
5	Recurrent carcinoma	41
6	Insufficient record	6
Total.....		192

applied for the eradication of primary tumor is given. The cases of recurrent carcinoma are included but are separately considered.

The analysis of these 192 cases and the study of the results to September 1936 seemed to indicate that the routine employment of preoperative irradiation might have value as an adjunct to the complete operation in the treatment of operable carcinoma of the female breast. In making microscopic studies I found no residual carcinoma in the breast or the axillary lymph nodes in 10 (24 per cent) of the 43 cases in which preoperative irradiation and the complete operation were done (group 1), although preoperative biopsy showed that the disease was present in 7 instances. Seventy-one per cent of the patients who were given this combined treatment were living and free from recurrence for an average of one year and ten months after the beginning of irradiation, while only 33 per cent of the 51 patients treated by the

1. Cohn, L. C.: Carcinoma of Female Breast, with Special Consideration of Preoperative Irradiation, Arch. Surg. 35:694-711 (Oct.) 1937.

complete operation without preoperative irradiation (group 2) were living and without clinical evidence of recurrence. In this group, however, an average of three years and four months, almost double the time in group 1, had elapsed since operation. Even after finding that carcinoma in the breast could be completely eradicated by irradiation therapy in almost 1 of 4 instances and after learning that more than twice as many patients survived after the combined treatment than after treatment by operation alone, I made the following statement with reference to the value of preoperative irradiation: "The solution of

TABLE 2.—*End Results for Patients in Group 1**

Total number of patients.....				43
Dead postoperatively from infection.....				1
Patients available for consideration of the ultimate result.....				42
	1936	1938	1941	
Living, free from recurrence.....	30 (71%)	28 (61%)	21 (50%)	
Average time since operation, 6 years				
Living, with recurrence.....	4} (28%)	1} (44%)	21 (50%)	
Dead from cancer.....	15}	19}		
Average time since operation, 2 yr. 6 mo.				
Under five years.....			18	
Over five years.....			3	
Five year cures.....			24 (57%)	

* In this and the following tables the end results are computed for a period ending Feb. 1, 1941.

TABLE 3.—*End Results for Patients in Group 2*

Total number of patients.....				51
	1936	1938	1941	
Living, free from recurrence.....	17 (33%)	13 (25%)	10 (19.6%)	
Average time since operation, 7 yr. 6 mo.				
Living, with recurrence.....	3} (60%)	2} (70%)	41 (80.4%)	
Dead from cancer.....	28}	34}		
Average time since operation, 2 yr. 11 mo.				
Under five years.....			33	
Over five years.....			8	
Five year cures.....			18 (35%)	

this problem, at least as far as this series of patients is concerned, will have to await the passage of time."

It is now more than five years since treatment was carried out in this series of cases, and I wish to present the accumulated evidence for and against the value of preoperative irradiation. The end results for the patients in group 1 are summarized in table 2, and the end results for the patients in group 2 are summarized in table 3. In these and the following tables patients remaining free from demonstrable evidence of recurrence or metastases for five years are classified as five year cures, even though they subsequently died of cancer.

Presumptive evidence in favor of the value of preoperative irradiation therapy as a part of the treatment for operable cancer of the breast is derived from a comparison of the gross figures for five year cures in groups 1 and 2. These figures are given in tables 2 and 3 as 57 and 35 per cent, respectively. For the purpose of analysis these figures

have been broken down and studied in relation to the presence or absence and the extent of regional metastasis and in relation to the grade of tumor. The figures in tables 4 and 5 indicate that in group 1 the axillary lymph nodes were free of metastasis in 56 per cent of the

TABLE 4.—*End Results in Relation to Regional Metastasis for Patients in Group 1*

Total number of patients.....	43
Patients with axillary lymph nodes not involved by metastasis.....	23 (56%)
Dead under five years from a cause other than cancer.....	1
Available for consideration of the ultimate result.....	22
Living and free from recurrence.....	18 (82%)
Average time since operation, 6 yr. 2 mo.	
Dead from cancer.....	4
Under five years.....	3
Over five years.....	1
Five year cures.....	19 (86%)
Axillary lymph nodes involved by metastasis.....	18 (42%)
Living and free from recurrence.....	1 (5.5%)
Dead from cancer.....	17
Under five years.....	15
Over five years.....	2
Five year cures.....	3 (17%)*
No note on involvement of lymph nodes.....	2

* One patient living with metastasis.

TABLE 5.—*End Results in Relation to Regional Metastasis for Patients in Group 2*

Total number of patients.....	51
Patients with axillary lymph nodes not involved by metastasis.....	14 (30%)
Dead under five years from a cause other than cancer.....	1
Available for consideration of the ultimate result.....	13
Living and free from recurrence.....	5 (38%)
Average time since operation, 7 yr. 9 mo.	
Dead.....	9
From cancer.....	6
Under five years.....	2
Over five years.....	4
From cause other than cancer.....	3
Under five years.....	1
Over five years.....	2
Five year cures.....	11 (85%)*
Patients with axillary lymph nodes involved by metastasis.....	33 (70%)
Living and free from recurrence.....	4 (12%)
Average time since operation, 6 yr. 6½ mo.	
Dead from cancer.....	29
Under five years.....	27
Over five years.....	2
Five year cures.....	6 (18%)
Patients with no note on involvement of lymph nodes.....	4

* One patient living with carcinoma of the pancreas.

cases, while in group 2 such was the case in only 30 per cent. It seems important to determine, and yet at the present time it is obscure, whether this variation in the percentage of regional metastasis in the two groups was due to the exposure of the lymph nodes of the patients in group 1 to irradiation. It seems significant that when the axillary lymph nodes were not involved by metastasis, the percentages of patients in the two groups remaining free of clinical evidence of the

disease for five years were almost identical—86 in group 1 and 85 in group 2. When the axillary lymph nodes were involved by metastasis, the five year cures were 17 per cent in group 1 and 18 per cent in group 2. These figures seem to indicate that the percentage of five year survivals is to a large extent determined by the presence or the absence of regional metastasis at the time of operation.

TABLE 6.—*End Results in Relation to the Extent of Regional Metastasis for Patients in Group 1*

Total number of patients.....	43
Patients with axillary lymph nodes involved by metastasis.....	18 (42%)
Patients with metastasis to basal axillary glands only.....	6
Living and free from recurrence.....	1
Dead from cancer.....	5
Under five years.....	4
Over five years.....	1
Five year cures.....	2 (33%)
Patients with metastasis to basal and middle axillary glands.....	1
Dead from cancer under five years.....	1
Five year cures.....	0
Patients with metastasis to basal, middle and highest apical axillary glands.....	7
Dead from cancer under five years.....	7
Five year cures.....	0
No note on the extent of regional metastasis.....	4

TABLE 7.—*End Results in Relation to the Extent of Regional Metastasis for Patients in Group 2*

Total number of patients.....	51
Patients with axillary lymph nodes involved by metastasis.....	33 (70%)
Patients with metastasis to basal axillary glands only.....	7
Living and free from recurrence.....	0
Dead from cancer.....	7
Under five years.....	6
Over five years.....	1
Five year cures.....	1 (14%)
Patients with metastasis to basal and middle axillary glands.....	6
Living and free from recurrence.....	2
Dead from cancer under five years.....	4
Five year cures.....	2 (33%)
Patients with metastasis to basal, middle and highest apical axillary glands.....	12
Living and free from recurrence.....	1
Dead from cancer under five years.....	11
Five year cures.....	1 (8%)
No note on the extent of regional metastasis.....	8

The end results in relation to the extent of involvement of the axillary lymph nodes are summarized in tables 6 and 7. The total of cases in each subgroup is too small for comparative study; yet the figures seem to indicate that even when there is extensive involvement of the axillary lymph nodes, the use of preoperative irradiation does not contribute toward increase in the number of five year cures.

The end results in relation to the grade of tumor are summarized in tables 8 and 9. In group 1 the actual and relative numbers of grade 1 tumors were far greater than in group 2; thus a basis for comparison

is lacking. However, reports in the literature and personal experiences convince me that five year cures approaching 90 per cent can be expected from treatment entirely by operation for patients harboring grade 1 tumor.

TABLE 8.—*End Results in Relation to Grade of Tumor for Patients in Group 1*

Total number of patients.....	43
Patients with grade 1 tumor.....	8
Living and free from recurrence.....	7 (90%)
Average time since operation, 5 yr. 10 mo.	
Dead from cancer under five years.....	1
Patients with grade 2 tumor.....	12
Living and free from recurrence.....	6
Average time since operation, 7 yr.	
Dead from cancer.....	6
Average time since operation, 2 yr. 6 mo.	
Under five years.....	4
Over five years.....	2
Five year cures.....	8 (66%)
Patients with grade 3 tumor.....	18
Living and free from recurrence.....	4
Average time since operation, 6 yr.	
Dead from cancer.....	14
Under five years.....	13
Over five years.....	1
Five year cures.....	5 (28%)
Patients with grade 4 tumor.....	2
Well five years.....	1
Dead from a cause other than cancer.....	1
Patients with unclassified tumor.....	3

TABLE 9.—*End Results in Relation to Grade of Tumor for Patients in Group 2*

Total number of patients.....	51
Patients with grade 1 tumor.....	2
Living and free from recurrence.....	0
Patients with grade 2 tumor.....	15
Living and free from recurrence.....	6
Average time since operation, 7 yr. 5 mo.	
Dead.....	9
From cancer.....	7
Average time since operation, 4 yr. 2 mo.	
Under five years.....	4
Over five years.....	3
From a cause other than cancer.....	2
Under five years.....	1
Over five years.....	1
Five year cures.....	10 (66%)
Patients with grade 3 tumor.....	29
Living and free from recurrence.....	4
Average time since operation, 7 yr.	
Dead from cancer.....	25
Under five years.....	21
Over five years.....	4
Five year cures.....	8 (27.5%)
Patients with grade 4 tumor.....	2
Dead from cancer.....	2
Patients with unclassified tumor.....	3

When the histologic picture of the tumor corresponded to grade 2, 66 per cent five year cures were obtained whether or not preoperative irradiation was used in conjunction with the operation. When the tumor was grade 3 from the histologic appearance, approximately 28

per cent five year cures resulted from treatment by either method. Four tumors because of their extreme anaplastic structure were placed in grade 4. Two of these tumors were in group 1 and two in group 2. The only five year cure was in group 1.

Group 3 consisted of 42 women with carcinoma of the breast treated by irradiation with roentgen rays or by a combination of roentgen rays and radium but not subjected to the complete operation (table 10). Thirty-eight of these were considered suitable for consideration of the

TABLE 10.—End Results for Patients in Group 3

Gross End Results	
Total number of patients.....	42
Lost from observation.....	3
Patients remaining for consideration of the gross end results.....	39
Living and free from recurrence.....	4 (10%)
Average time since the beginning of irradiation, 7 yr. 9 mo.	
Dead.....	35
From a cause other than cancer.....	2
Under five years.....	1
Over five years.....	1
From cancer.....	33
Average duration of life since the beginning of irradiation, 1 yr. 6 mo.	
Under five years.....	32
Over five years (patient subjected to complete operation for recurrence).....	1
Five year cures.....	6 (16%)
End Results in Relation to Operability of Tumor	
Total number of patients.....	42
Lost from observation.....	3
Patient subjected to complete operation after recurrence.....	1
Patients remaining for consideration of end results.....	38
A. Patients with inoperable tumor.....	27
Living more than five years.....	1
Dead from cancer under five years.....	26
Five year cures.....	1 (4%)
B. Patients with operable tumor.....	11
Living and free from recurrence.....	3
Dead.....	8
From a cause other than cancer.....	2
Under five years.....	1
Over five years.....	1
From cancer.....	6
Under five years.....	6
Five year cures.....	4 (30%)

end results. The gross five year cures in this group were 16 per cent. Twenty-seven tumors (70 per cent) were considered inoperable because of the extent of the local and regional involvement or because of the presence of distant metastasis when the patient was first examined (A, table 10). Twenty-six of these patients died from cancer within five years, and only 1 (4 per cent) is still alive at the time of writing. There were 11 patients with operable tumor on whom it would have been feasible to perform the complete operation, but for various reasons the operation was restricted to biopsy or to excision of the tumor in 8 cases. There was no biopsy in 3 cases. The breast, the axilla and the supraclavicular area of each patient were treated by irradiation. The five year cures in this group were 36 per cent. In each of the 3

instances in which the patient is living and free from evidence of recurrence for more than five years at the time of writing, the tumor had been excised and considered on microscopic study to be low grade. Two of these tumors were colloid carcinoma; the other was adenocarcinoma of the sweat gland type. One patient died more than five years after irradiation therapy from a cause other than cancer. When first examined she was 76 years of age and had been aware of the presence of the tumor of the breast for one month. This tumor, which was clinically malignant, rapidly disappeared under irradiation therapy. However, there was no biopsy to confirm the clinical diagnosis of cancer.

The end results in group 4 are given in table 11. This group comprised those patients whose breast was excised by a restricted

TABLE 11.—*End Results for Patients in Group 4*

Total number of patients.....	9
Patients given preoperative irradiation.....	4
Dead from cancer under five years.....	1
Living and free from recurrence.....	3 (75%)
Patients given no irradiation.....	5
Dead.....	4
From cancer under five years.....	3
From a cause other than cancer under five years.....	1
Living and free from recurrence.....	1 (25%)
Five year cures.....	4 (50%)

TABLE 12.—*End Results for Patients in Group 5*

Total number of patients.....	41
Dead under five years for a cause other than cancer.....	1
Patients remaining for consideration of the end result.....	40
Living and free from recurrence.....	0
Dead from cancer.....	40
Average duration of life after first examination, 1 yr 4½ mo.....	
Five year cures.....	0

operation, the extent of which did not conform to the standards set for the complete operation. In all but 1 instance the extent of the operation exceeded that of simple mastectomy and consisted of the excision of the breast and the pectoral muscles or the excision of the breast and the axillary lymph nodes but not of the pectoral muscles. The gross five year cures in this group were 50 per cent. The number of cases are too few and the operations too unlike for comparison. Three of the 4 patients (75 per cent) receiving preoperative irradiation are living and free from recurrence for more than five years after operation at the time of writing. The tumor in 1 instance was comedo-adenocarcinoma and in 2 cases grade 2 scirrhus carcinoma. One of the 5 patients, whose treatment was entirely surgical, died under five years from a cause other than cancer. Three died from cancer. One (25 per cent) is living and free from recurrence at the time of writing. This tumor was grade 3 scirrhus carcinoma.

SUMMARY AND CONCLUSIONS

The five year cures among 94 patients with carcinoma of the breast subjected to the complete operation are calculated to be 45 per cent (table 13). In 51 of these cases the treatment was entirely surgical, and the five year cures in this group were 35 per cent. In 43 cases, preoperative irradiation was used in conjunction with the surgical treatment, and the five year cures were 57 per cent. Analysis seems to indicate that the end results have been largely determined by the grade of the tumor and the condition of the axillary lymph nodes at the time of operation. From the study of my material I am unable to state whether or not the condition of the axillary lymph nodes and the grade of the tumor were modified when preoperative irradiation was

TABLE 13.—*Gross Five Year Cures*

Groups 1 and 2	
Total number of patients.....	94
Postoperative death from infection.....	1
Patients available for consideration of the ultimate result.....	93
Five year cures.....	42 (45%)
Groups 3B and 4	
Total number of patients.....	20
Death from a cause other than cancer under five years.....	1
Patients available for consideration of the ultimate result.....	19
Five year cures.....	8 (42%)
Group 3A and 5	
Total number of patients.....	68
Death from a cause other than cancer under five years.....	1
Patients available for consideration of the ultimate result.....	67
Five year cures	1 (<1%)

used. The solution of this problem would certainly permit a more accurate estimate of the value of preoperative irradiation.

The five year cures in a group of 20 operable patients not subjected to the complete operation are calculated to be 42 per cent. The survivors are composed of patients treated by simple excision of the tumor followed by irradiation therapy or by amputation of the breast in a restricted operation. The majority of the latter received preoperative irradiation. The relatively large number of survivors seems to have been greatly influenced by the presence in this group of a large percentage of low grade tumors, and there is also some evidence that irradiation therapy has influenced the end results.

The five year cures in 68 cases of inoperable and recurrent carcinoma of the breast are calculated to be less than 1 per cent. Analysis reveals no actual evidence that the end results have been materially modified by the use of irradiation therapy in 67 of the cases.

SARCOMA OF THE BREAST

ROBERT P. HILL, M.D.

AND

ARTHUR PURDY STOUT, M.D.

NEW YORK

The development of knowledge of sarcoma of the breast has been handicapped by confusion in classification, a state still prevalent to some extent. This has been due chiefly to the striking variability of the manifestations of sarcoma of the breast (in contrast to the uniformity exhibited by sarcoma in other regions) and to the infrequency of its occurrence—factors all too apparent in any review of the subject in which there is an attempt to place the various forms in well defined groups.

The older literature contains numerous examples of so-called breast sarcoma classified with little regard to histogenesis and subsequent course but largely on gross or microscopic appearance. The prevailing tendency was to name the neoplasms according to the morphologic characteristics of the component elements; the result was the development of a multitude of terms, most of which convey little information as to the tissue of origin. Therefore, although one can speculate, it is difficult and often impossible to be certain of exactly what such tumors were. It also seems unquestioned that in the past the term "sarcoma" has been used loosely as a convenient category for those neoplasms that were not frankly epithelial in nature. Thus, there has been a steady decline in the reputed frequency as more and more atypical forms of carcinoma, benign tumors and the like have been excluded from the general group. Today the incidence is given as between 0.5 and 3 per cent of all malignant breast tumors¹ in contrast to an incidence of 6 to 9 per cent in the earlier

From the Surgical Pathology Laboratory of the Columbia University College of Physicians and Surgeons and the Department of Surgery of the Presbyterian Hospital and Sloane Hospital for Women.

1. Boldrey, E. B.: Primary Sarcoma of the Breast, with Report of Four Cases, *Canad. M. A. J.* **35**:16, 1936. Fox, S. L.: Sarcoma of the Breast: Report of Sixty Cases, *Ann. Surg.* **100**:401, 1934. Pack, G. T., and LeFevre, R. G.: The Age and Sex Distribution and Incidence of Neoplastic Diseases at the Memorial Hospital, New York City, *J. Cancer Research* **14**:167, 1930. Rose, J.: Die Sarkome der weiblichen und die Geschwülste der männlichen Brustdrüsen nach dem Material der chirurgischen Klinik zu Leipzig, *Deutsche Ztschr. f. Chir.*

(Footnote continued on next page)

reports. The latter figures, however, can be reduced to 5 or 6 per cent if instances of cystosarcoma are eliminated. One of the important reasons for this decrease has been the greater realization in recent years of the degree to which cancer cells can assume a spindle shape, and it is now known that such an appearance alone does not necessarily imply sarcoma. Likewise, an alveolar arrangement should suggest at once that the primary change is epithelial in type. It also seems probable that many of the neoplasms formerly designated as round cell sarcoma, perithelioma, cylindroma and angiosarcoma are really carcinoma.

An interesting group of breast neoplasms often incorporated with the sarcoma group was first isolated by Müller in 1838.² He recognized their benign clinical course and described three varieties to which he gave the names of simple cystosarcoma, cystosarcoma proliferum and cystosarcoma phyllodes. Two years later, Brodie³ discussed this same group and mentioned five different stages in the evolution of the tumors. It is likely that Müller's three varieties represented various stages in the development of the same type of neoplasm, a view considered probable by Delbet.⁴ Other writers also recognized this particular tumor type and described it under different names; all more or less realized the usually innocent nature of the disease. In 1931, Lee and Pack⁵ found 105 examples of this type of tumor in the literature and added 6 more. They recommended the term "giant intracanalicular fibro-adenomyxoma" for it and discussed its characteristics in detail.

One of the first great attempts to segregate the varieties of mammary sarcoma into an organized classification was that of Gross in 1887.⁶ He collected 156 cases in all, including 19 of his own. Although he divided sarcoma into three principal forms (spindle, round and giant cell), he had fourteen subvarieties. The differentiation was based largely on morphologic grounds, and for present day purposes this work is of little value except for consideration of the group as a whole.

246:151, 1936. Sailer, S.: Sarcoma of the Breast, *Am. J. Cancer* **31**:183, 1937. Schreiner, B. F., and Thibaudeau, M. B.: Sarcoma of the Breast, *Ann. Surg.* **95**:433, 1932. Smith, G. Van S., and Bartlett, M. K.: Malignant Tumors of the Female Breast, *Surg., Gynec. & Obst.* **48**:314, 1929.

2. Müller, J.: Ueber den feinern Bau und die Formen der krankhaften Geschwülste, Berlin, G. Reimer, 1838, p. 56.

3. Brodie, B. M.: Lectures on Sero-Cystic Tumours of the Breast, London *M. Gaz.* **25**:808, 1840; reprinted, *M. Classics* **2**:941, 1938.

4. Delbet, P.: Tumeurs de la mamelle, in Duplay, S., and Reclus, P.: *Traité de chirurgie*, ed. 2, Paris, Masson & Cie, 1897, vol. 5, pp. 875-906.

5. Lee, B. J., and Pack, G. T.: Giant Intracanalicular Myxoma of the Breast, *Ann. Surg.* **93**:250, 1931; Giant Intracanalicular Fibro-Adenomyxoma of the Breast: The So-Called Cystosarcoma Phyllodes Mammæ of Johannes Müller, *Am. J. Cancer* **15**:2583, 1931.

6. Gross, S. W.: Sarcoma of the Female Breast, *Am. J. M. Sc.* **94**:2, 1887.

In 1894, Williams,⁷ from a collection of 1,091 cases of sarcoma, found 99 involving the breast. Thirty of these cases formed the basis for his observations, and he divided them into cases of pure sarcoma and cases of adenosarcoma. In 1915, Geist and Wilensky⁸ reviewed the subject and going as far back in the literature as 1858 found 423 cases of breast sarcoma. In the final tabulation of these cases, twenty different forms were listed. At the same time, they added 22 examples which they classified as spindle cell sarcoma, round cell sarcoma, giant cell sarcoma, cystosarcoma, fibrosarcoma and perithelioma.

There were many other contributions on this subject during the latter part of the nineteenth and the first part of the twentieth century, but in most of them the classifications were more descriptive than practical. Although these reports have been reviewed, the information contained in them is usually too equivocal to be used in an analysis of these neoplasms.

In the past mammary sarcoma has been divided rather arbitrarily into adenosarcoma and pure sarcoma, and for this study a somewhat similar separation has been maintained. The latter group, however, can be separated into several specific types. Accordingly we have made the following classification:

1. Adenofibrosarcoma (cystosarcoma phyllodes)
2. Fibrosarcoma
3. Lymphoblastoma
4. Malignant hemangioendothelioma
5. Liposarcoma and myosarcoma
6. Mixed tumor

During the years between 1911 and 1940, inclusive, 15 cases of adenosarcoma, 5 of fibrosarcoma, 2 of lymphosarcoma, 2 of leukemic tumor, 2 of carcinosarcoma (?) and 2 of malignant hemangioendothelioma of the mammary gland have been recorded in the Surgical Pathology Laboratory of Columbia University College of Physicians and Surgeons. In this same period there have been 1,990 cases of carcinoma. Thus sarcoma is represented in 1.2 per cent of all malignant mammary tumors without incorporation of the leukemias. If adenosarcoma is eliminated from the malignant class, true sarcoma forms only 0.4 per cent of malignant mammary growths. All of these mammary tumors appeared in females.

7. Williams, W. R.: *Diseases of the Breast*, London, John Bale & Sons, 1894, p. 417.

8. Geist, S. H., and Wilensky, A. O.: *Sarcoma of the Breast*, *Ann. Surg.* 62:11, 1915.

ADENOFIBROSARCOMA

The term "adenofibrosarcoma" has been retained because through usage it has become associated with a specific tumor type, but we realize that the epithelial elements play only a passive part in the neoplastic process. Further, the usual benign course of the disease is recognized, and it is questionable if this type of tumor should be called sarcoma at all. However, its sometimes close association with fibrosarcoma and its frequent incorporation in the general group have seemed sufficient justification for its inclusion.

Adenofibrosarcoma develops in two principal ways. In the first, a sarcomatous change takes place in a pericanalicular fibroadenoma with the production of the tumor type often designated as adenosarcoma or adenofibrosarcoma. In the second, the change occurs in an intracanalicular fibroadenoma and constitutes the form commonly called cystosarcoma phyllodes or cystosarcoma. The latter form sometimes reaches an enormous size; this is exemplified in the frequently quoted case of Velpeau in which the tumor attained a weight of 20 Kg.

Adenofibrosarcoma appears most frequently during the fifth decade, but it may be found during any period of life following puberty. It accounts for less than 1 per cent of all mammary tumors⁹ but is the form of sarcoma most frequently observed.

The symptoms are fairly characteristic. There is usually a history of a preceding lump which, having remained stationary or having slowly increased in size for a variable period of years, suddenly becomes transformed into a rapidly enlarging mass—a change sometimes initiated by trauma. Occasionally, growth is rapid from the beginning. Although the growth is usually single, multiple nodules are sometimes observed, and rarely the disease may be bilateral. The chief signs of carcinoma, i. e., nipple retraction, cutaneous edema and fixation, are generally lacking. Ulceration of the skin and pain are late symptoms and develop only after the tumor has attained an immense size. These skin changes, if present, are a result of pressure atrophy and do not represent true invasion.

On examination, the tumor appears as a well circumscribed, freely movable and sometimes cystic mass. The surface is usually smooth, although in the larger growths it may be indefinitely nodular (fig. 1). The axillary nodes are small, soft and freely movable, except when enlarged owing to inflammatory hyperplasia.

9. Funck-Brentano, P.; Bertrand, I., and Poilleux, F.: Les tumeurs phyllodes du sein. (Cystosarcoma phyllodes de Johann Müller), *J. de chir.* **51**:506, 1938. Greenough, R. B., and Simmons, C. C.: Fibro-Epithelial Tumors of the Mammary Gland, *Ann. Surg.* **54**:517, 1911. Warren, J. C.: The Surgeon and the Pathologist, *J. A. M. A.* **45**:149 (July 15) 1905.

Grossly, the tumor is spherical and encapsulated; ramifications of the capsule often extend into the substance and form indefinite lobules or nodules. The surface is frequently uneven and irregular. The consistency is variable but usually moderately firm, unless extensive necrosis and cyst formation have supervened. The cut surface is bulging, grayish white or pinkish gray, whorled and elastic. In the intracanalicular variety, the growth is traversed by clefts into which polypoid masses



Fig. 1 (case 6)—Adenofibrosarcoma. A typical example is shown. Note the large size, the spherical shape and the nodular surface of the tumor. The skin is thin and stretched and the nipple flattened, but these structures are not invaded.

may project so that these clefts have a branched or stellate appearance (fig. 2). Cysts, if present, are of two types: (1) those resulting from continued secretion of the epithelial cells and lined by a smooth glistening membrane; (2) those produced by necrosis and liquefaction. The pericanalicular type is usually smaller, firmer and seldom cystic. Sometimes, the remnants of a preexisting fibroadenoma can be distinguished.

Microscopically, the picture is variable, although there are two extremes between which all gradations occur. At the one extreme the similarity to fibroadenoma is well retained; the only difference is in the increased cellularity of the stroma and the presence of scattered mitoses and bizarre cell forms. Myxomatous changes often occur, and Lee and Pack⁵ stated that "the metaplasia of the stroma into such tissue is the distinguishing and essential feature of the intracanalicular variety." The epithelial components may be scarce or fairly prominent, but hyperplasia is infrequent. Squamous metaplasia sometimes occurs, and occasionally epithelial pearls are formed. At the other extreme is a



Fig. 2 (case 6).—Adenofibrosarcoma. The tumor is encapsulated and cystic. Smooth-lined polypoid masses often project into the cysts and the clefts.

highly cellular appearance, the tumor being composed of indefinitely spindle or polymorphous cells separated by little collagen. Mitoses, giant cells and atypical cells are numerous, and the stroma has a true sarcomatous appearance. The epithelial elements form only a minor part of the structure, are widely scattered and in some parts of the tumor may be lacking. As a rule, the majority of the neoplasms fall somewhere between these two extremes.

The sarcomatous change may be diffuse and fairly uniform throughout the fibroadenoma, so that the entire mass appears to have been trans-

formed at the same time. Tumors of a certain group, however, have a patchy appearance in that parts of the tumor are highly cellular, while other portions are relatively acellular and hyalinized. The impression is gained thereby that fibroadenoma is being replaced by sarcoma originating from a single focus within it (fig. 3). Although most of the tumors are bounded by a compression capsule, direct contact with the adjacent fat may be present. The surrounding portion of the breast shows no changes which are constant or characteristic.

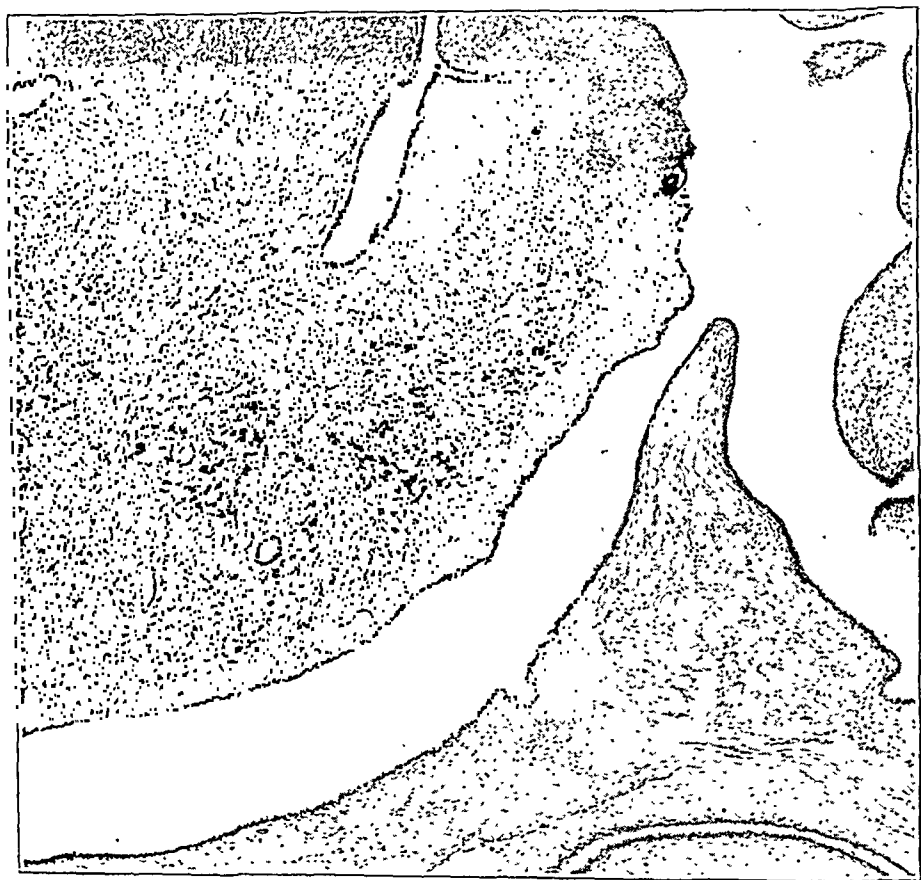


Fig. 3 (case 2).—Adenofibrosarcoma. A characteristic intracanalicular fibroadenoma with uneven distribution of the sarcomatous transformation is shown. Note the uninvolved zone just beneath the epithelium.

As to prognosis, most observers agree on the generally innocent course of the disease. Distant metastasis has been reported by Billroth,¹⁰

10. Billroth, T.: Diseases of the Female Mammary Glands, in Grandin, E. H.: Cyclopaedia of Obstetrics and Gynecology, New York, William Wood & Company, 1887, vol. 9, pp. 51, 56 and 71.

Prym,¹¹ Sophian,¹² Fox, Guérin¹³ and Johnsrud,¹⁴ but it is a rare complication. Metastasis to the axilla probably never occurs. Local recurrence followed by metastasis has been noted¹⁵; the tumors usually recur as fibrosarcoma and metastasize in this form. Local recurrence alone is supposedly more common, and some of the first writers on the subject had strikingly high percentages for this feature. However, Lee and Pack found only 6 recurrences in 91 reported cases in which the outcome was known, and Harrington and Miller¹⁶ observed this complication in only 1 of 24 cases of fibroadenoma. It seems unlikely that recurrence plays a prominent role except in a small number of cases. Further, there is always the possibility that apparent recurrence may represent an entirely new tumor.

Local excision is adequate therapy unless the tumor is exceptionally large; this is a factor which sometimes necessitates a more extensive procedure for complete removal of the growth. Should recurrence appear, it is probably better then to perform simple mastectomy. There is no way to determine which tumors of this group will show malignant tendencies; only the subsequent course of the patient can answer the question. The chief danger is that the tumor in question may recur as fibrosarcoma with the correspondingly increased threat of distant spread.

In this laboratory 15 tumors have been accepted as belonging to this class. Certain large cellular growths classed as fibroadenoma but showing none of the cellular changes commonly associated with malignant tumor have been excluded. The 15 tumors mentioned constitute 2.1 per

11. Prym, P.: Fibrocystadenoma sarkomatosum der Mamma mit Metastasen, *Frankfurt. Ztschr. f. Path.* **10**:60, 1912.

12. Sophian, L. H.: Adenofibrosarcoma of the Breast, *Arch. Path.* **9**:1007 (May) 1930.

13. Guérin, P.: Sarcome à cellules géantes du sein par transformation d'un fibro-adénome latent, *Bull. Assoc. franç. p. l'étude du cancer* **25**:326, 1936.

14. Johnsrud, R. L.: Sarcoma of Breast, *Northwest Med.* **39**:27, 1940.

15. (a) Finsterer, J.: Ueber das Sarkom der weiblichen Brustdrüse, *Deutsche Ztschr. f. Chir.* **86**:352, 1906-1907. (b) Hartmann, H.; Bertrand-Fontaine, T., and Guérin, P.: Sur trois cas de sarcomes à cellules géantes du sein, *Bull. Assoc. franç. p. l'étude du cancer* **22**:378, 1933. (c) Hoffmann, A.: Ein durch die grosse Zahl der Recidive, sowie durch einen ausnahmsweise langdauernden recidivfreien Intervall bemerkenswerther Fall von Mammasarcom, *Arch. f. klin. Chir.* **48**:93, 1894. (d) White, J. W.: Malignant Variant of Cystosarcoma Phyllodes, *Am. J. Cancer* **40**:458, 1940. Sophian.¹²

16. Harrington, S. W., and Miller, J. M.: Lymphosarcoma of the Mammary Gland, *Am. J. Surg.* **48**:346, 1940; Fibrosarcoma of the Mammary Gland, *Surgery* **7**:129, 1940; Malignant Changes in Fibroadenoma of the Mammary Gland, *Surg., Gynec. & Obst.* **70**:615, 1940; A Mixed Tumor (Carcinosarcoma) of the Breast, *Surgery* **7**:122, 1940.

cent of all tumors removed with the diagnosis of fibroadenoma. The average age of the patients was 47.3 years, with extremes of 33 and 69 years. Ten tumors belonged to the intracanalicular variety; 2 were of mixed types, 2 were undetermined, and 1 was of the pericanalicular type. The average duration of symptoms was seventeen and eight-tenths

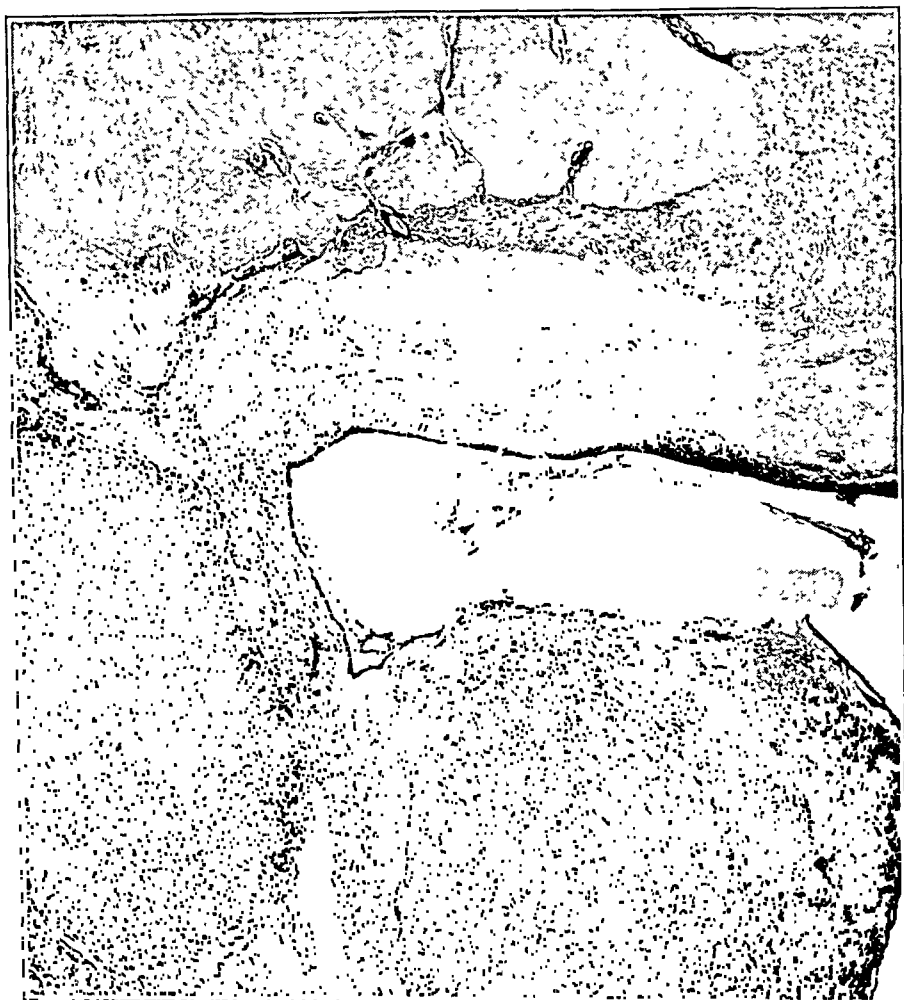


Fig. 4 (case 15).—Intracanalicular fibroadenoma with focal sarcomatous changes. There are areas of cartilaginous metaplasia both within the actively growing and within the acellular parts.

months, with one exception, a tumor which had been present for forty-two years. The period of rapid growth, however, averaged only six months, varying between one and twelve months. The smallest tumor was 3.5 cm. in diameter; the largest weighed 14 pounds (6.4 Kg.).

Seven of the patients were subjected to radical mastectomy, 5 had simple mastectomy, and 3 had only local excision. In no case in which the axilla was removed was there involvement of the lymph nodes. Nine patients have been followed, 5 have been lost sight of, and 1 died after operation. Six patients have lived from six to nineteen years without evidence of recurrence or metastasis, 1 died four years after operation from intercurrent causes, and 2 others are living after eighteen and twenty-five months without return of their disease. There was squamous metaplasia of the epithelium in 3 cases, and cartilaginous metaplasia of the stroma in 2 (figs. 4 and 5).

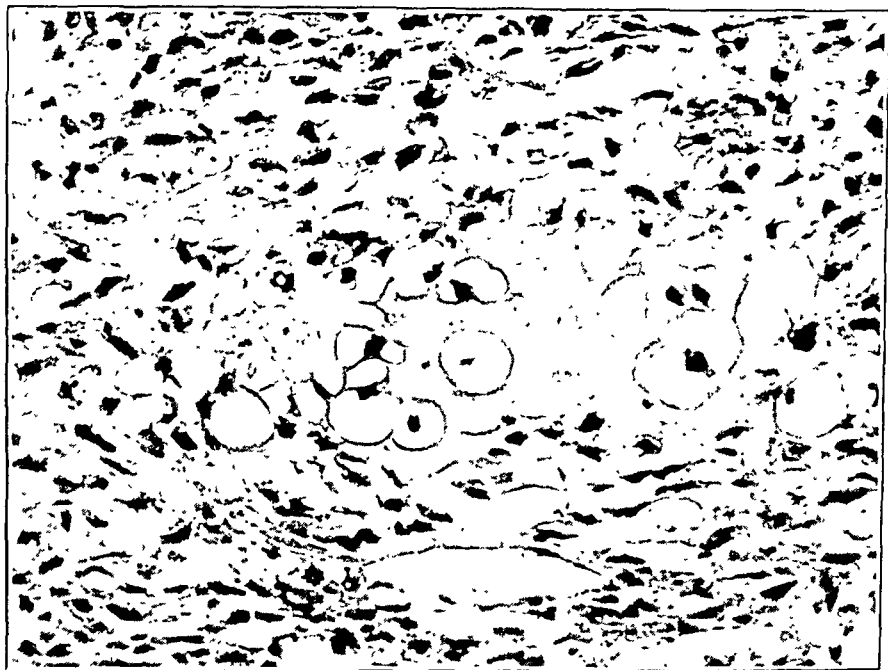


Fig. 5 (case 14).—Adenofibrosarcoma. Note a metaplastic focus of cartilage among the tumor cells.

FIBROSARCOMA

Fibrosarcoma is the most frequently encountered variety of pure sarcoma, but, even so, the number of cases is small. It originates from the ordinary connective tissue of the breast, i. e., the interlobar and interlobular fibrous tissues, and its behavior is similar to that of fibrosarcoma elsewhere.

The spindle cell, polymorphous cell, round cell, mixed cell, neurogenic and osteoid types of sarcoma, as well as myxosarcoma, are considered here, since most of them are primarily derived from connective tissue

and simply represent poor differentiation with the result that the fibroblastic nature of the growth is less evident. The majority of the round cell growths are probably lymphosarcoma and atypical carcinoma, although a few may be highly undifferentiated fibrosarcoma (fig. 6). There is no necessity to retain the term "myxosarcoma" since this ordinarily denotes a degenerative change in what is otherwise fibrosarcoma or adenosarcoma. Neurogenic sarcoma has been reported by Fox, Sailer and Stewart and Copeland,¹⁷ but it is closely allied to fibrosarcoma, and there seems little need to keep this subdivision. Further,

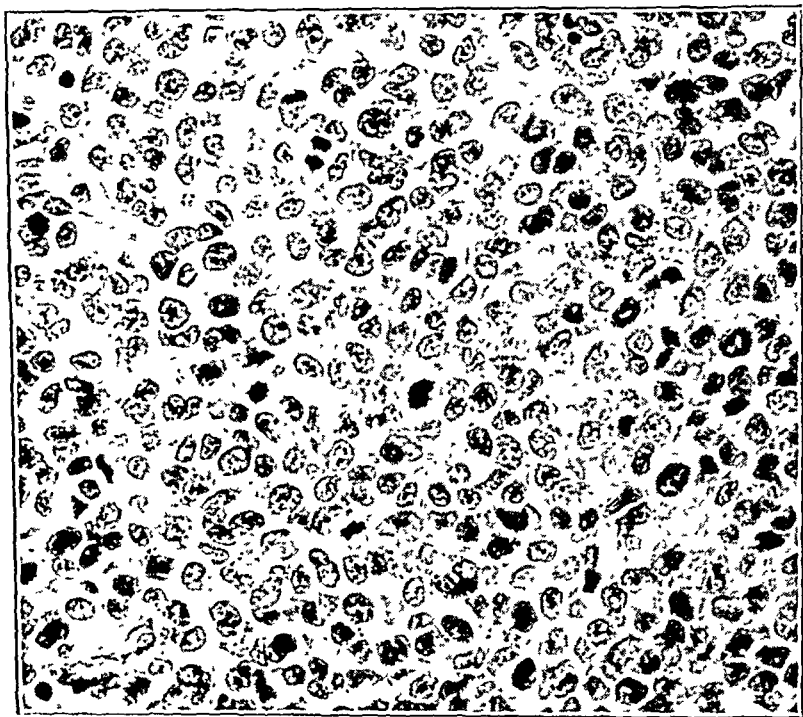


Fig. 6 (case 20).—Fibrosarcoma. The primary tumor composed of rounded cells is shown; its true nature was recognized only in the recurrence (see fig. 7).

if one accepts the theory of metaplasia, most tumors classified as osteoid chondrosarcoma or osteochondrosarcoma can be considered primarily fibrosarcoma with secondary development of osseous or cartilaginous tissue and thus are better classified as fibrosarcoma with osteoid metaplasia or as teratoid tumors. It is seldom necessary to explain their development on the basis of teratoma.

17. Stewart, F. W., and Copeland, M. M.: Neurogenic Sarcoma, *Am. J. Cancer* 15:1235, 1931.

Fibrosarcoma may occur at any age. Sheild¹⁸ noted myxosarcoma in the breast of an infant 6 months old. At the other extreme is the observation of Graves¹⁹ of a 12 pound (5.4 Kg.) spindle cell sarcoma in a 98 year old woman who ultimately died from pulmonary metastases. In most cases fibrosarcoma develops between the ages of 35 and 65 years, with an average age of 45 to 50 years, and therefore somewhat earlier in life than carcinoma.²⁰

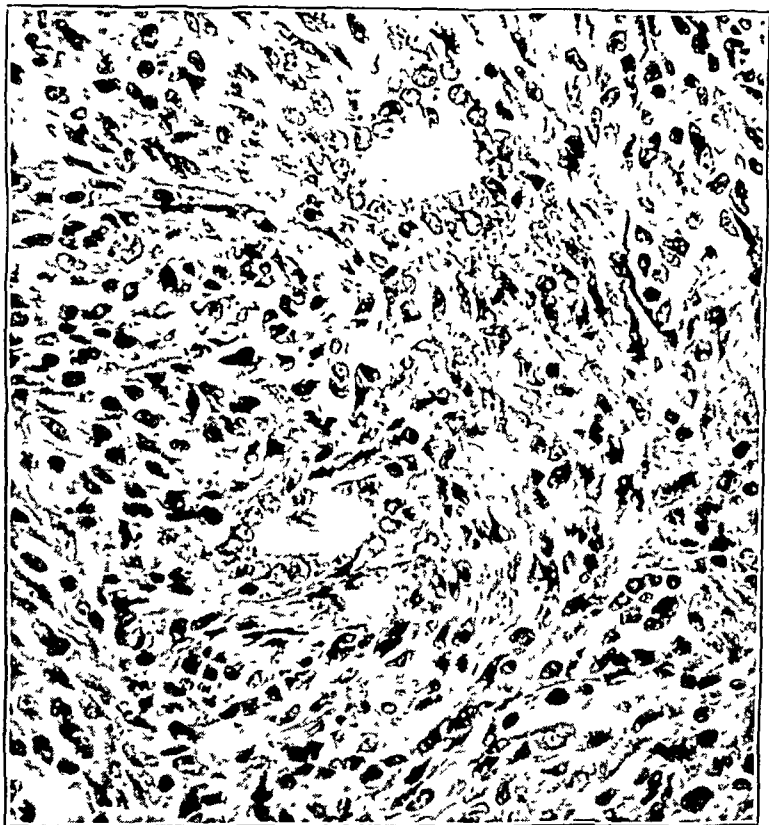


Fig. 7 (case 20) —Fibrosarcoma. A recurrent nodule with the tumor cells now spindle shaped and with intercellular collagen fibers indicating its fibroblastic character. Two incorporated ducts are present.

Although the vast majority of the tumors diagnosed as fibrosarcoma occur in females, a few are found in males and form a proportionately

18. Sheild, A. M.: *Diseases of the Breast*, London, Macmillan & Company, 1898, p 264.

19. Graves, T. C.: *Mammary Sarcoma of Old Age*, *Brit. M. J.* 1:81, 1920.

20. Deaver, J. B., and McFarland, J.: *The Breast: Its Anomalies, Its Diseases, and Their Treatment*, Philadelphia, P. Blakiston's Son & Co., 1917, pp. 372-442.

higher percentage of the total number of benign or malignant neoplasms. Neal²¹ found 10 tumors classified as sarcoma among 308 mammary lesions in males and 5 of these were fibrosarcoma. They appeared in a younger age group than did the tumors classified as carcinoma.

The symptoms are much the same as for adenosarcoma, and it is often impossible to differentiate between the two neoplasms. Ordinarily fibrosarcoma shows a greater tendency toward slow progressive enlarge-

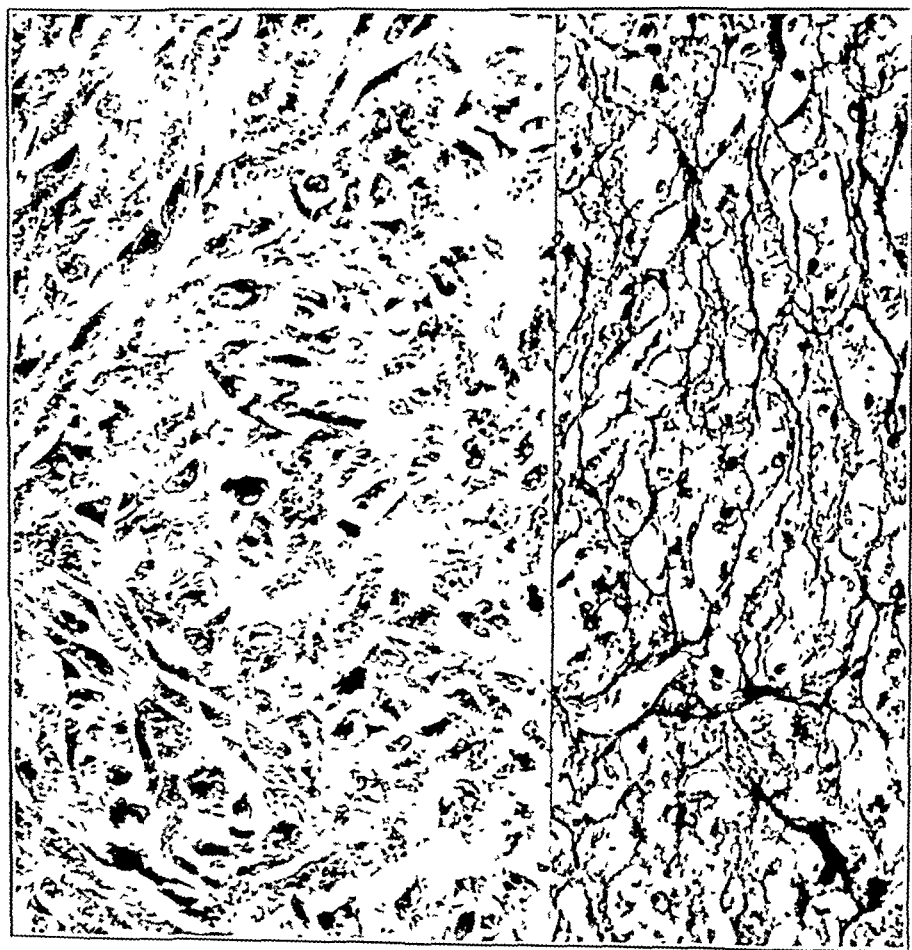


Fig. 8 (case 17).—Fibrosarcoma. The anaplastic cellular structure is shown on the left; on the right a Laidlaw silver reticulin stain shows connective tissue fibers wrapped around the tumor cells.

ment from the beginning, and the sometimes huge size of adenosarcoma is seldom seen, although large tumors have been observed.²² It is a firm

21. Neal, M. P.: Malignant Tumors of the Male Breast, *South. M. J.* **25**:841, 1932.

22. Cathcart, R. S.: Massive Sarcoma of Breasts, *South. Med. & Surg.* **92**: S10, 1930.

well circumscribed solid tumor which is usually freely movable and seldom adherent to the skin or the pectoral fascia.

Grossly, it is a well outlined, moderately firm spherical tumor having a more or less homogeneous grayish white to pinkish gray bulging cut surface. Clefts and cysts as found in adenosarcoma are not seen. The tissue not infrequently has an irregular whorled appearance, and foci of necrosis and hemorrhage may be present.

Microscopically, the picture is dependent on the degree of differentiation. In the better differentiated fibrosarcoma, the resemblance to

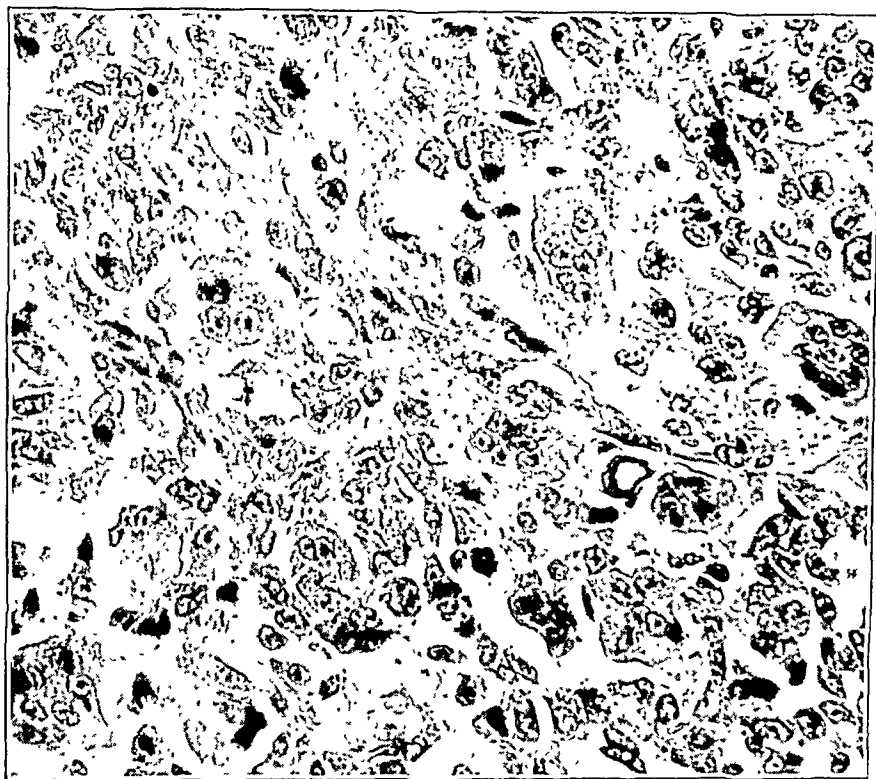


Fig. 9 (case 20).—Fibrosarcoma. Another area from a recurrent nodule showing the presence of numerous giant cells.

fibroma is marked, while in the undifferentiated and anaplastic forms, cellular pleomorphism, mitotic figures and giant cells are prominent features (fig. 8). Giant cells, if present, are of two varieties: (1) the true tumor giant cell, formed as a result of rapid growth and incomplete cell division after nuclear division, and (2) the foreign body giant cell, produced as a reaction to cellular necrosis, osteoid formation and similar changes. Sometimes giant cells may be exceptionally numerous, but there is no necessity to designate the neoplasms in which they are seen

as giant cell sarcoma (fig. 9). Epithelial elements are generally lacking but, if found, are represented by atrophic ducts incorporated in the periphery of the growth (fig. 10). Occasionally there are extensive bands of necrosis so that viable tumor cells are localized to the vicinity of blood vessels, and this feature has led to the mistaken diagnosis of perithelioma or angiosarcoma. Foci of osseous, osteoid or cartilaginous tissue are sometimes seen (fig. 11). Although usually encapsulated, the neoplasm may extend directly into the adjacent fat.

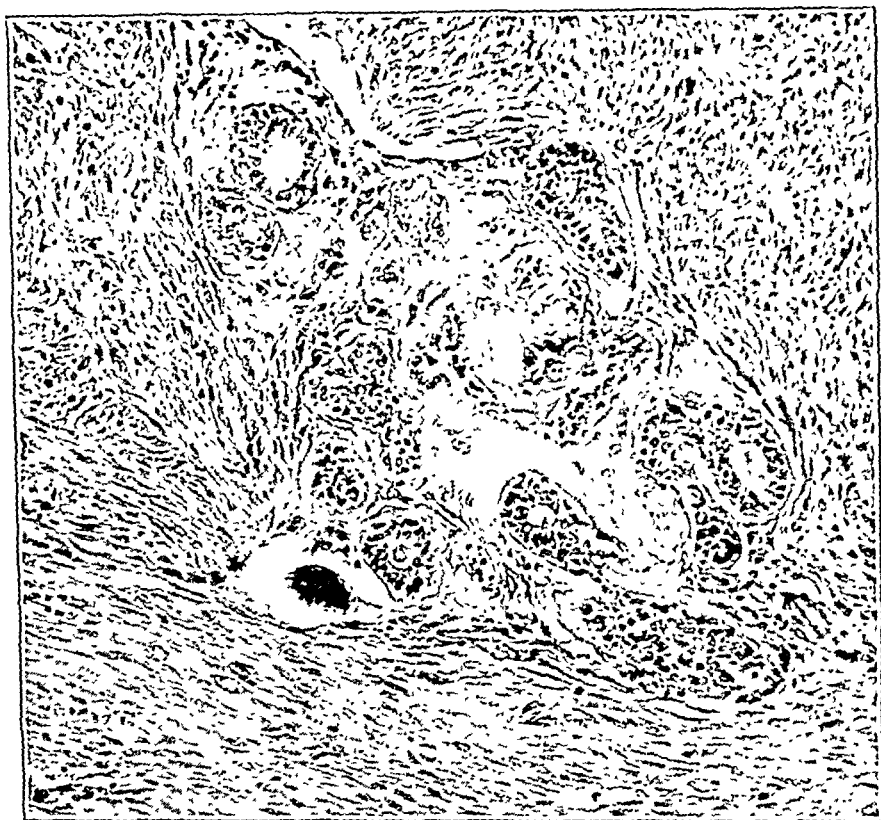


Fig. 10 (case 18).—A differentiated fibrosarcoma with incorporation of mammary ducts at its periphery. Although these ducts are compressed and atrophic, they maintain their usual lobular arrangement.

The tendency toward recurrence and metastasis is much greater than that in adenosarcoma, but the degree of malignancy is less than that of carcinoma. Metastasis, when it occurs, does so by way of the blood stream, and the lungs are the most frequent site. In 3 of 5 cases reported by Schreiner and Thibaudeau metastasis developed, and in a single case involving the male breast death occurred. In 4 of 9 cases reported by Harrington and Miller there was no evidence of the disease after four to seventeen years. In 2 of these 4, locally recurrent tumors had been

removed, and in 1 of the other 2 cases death ultimately resulted from the disease. Boldrey noted recurrences in 2 of 4 cases. Among 15 patients with fibrosarcoma whose cases were recorded by Finsterer, there were 4 who were free from recurrence, 3 who had local recurrences, 3 who suffered internal metastasis and 5 who were unknown or dead from intercurrent causes. Fox stated that a fatal termination occurred in 26.7 per cent of his cases but that only 33.3 per cent of the patients were

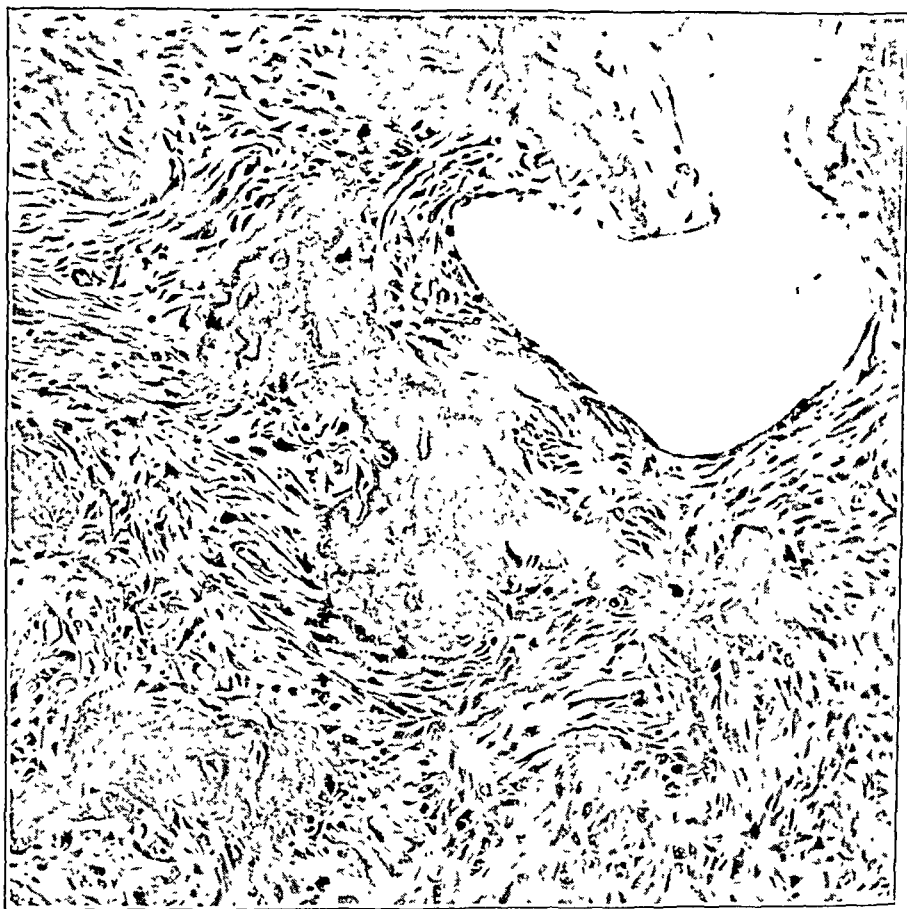


Fig. 11 (case 18).—Fibrosarcoma, showing the formation of osteoid tissue near the center. The adjacent tumor tissue merges almost imperceptibly with the osteoid elements.

known to be alive more than one year, while the mortality rate in cases of neurogenic sarcoma was 42.9 per cent. Rose, however, found that 5 patients out of 6 were living after one to twenty-three years, while the sixth had died six months after operation. An interesting case of local recurrence is that reported by Smith and Bartlett in which twenty-seven operations in all were undertaken for the primary and the recurrent growths; death finally resulted five years after the first operation.

Mastectomy with removal of the pectoral muscles is recommended by most writers as the method of choice, since the tumor may extend beyond the confines of its capsule. Wide local excision, though, has sometimes been employed with success. Repeated recurrence need not necessarily imply a hopeless outlook, since there is the case of Gross²³ in which the patient was subjected to twenty-three operations with removal of fifty-one separate tumors and final complete eradication of the disease. When the condition does progress to a fatal termination, it ordinarily has a more protracted course than carcinoma.

Our observations include 5 tumors diagnosed as fibrosarcoma. Three were well differentiated, and 2 were poorly differentiated. Four of the patients have been followed, and 2 are living and well without recurrent or metastatic disease after six and eleven years, respectively. Another patient is living five years after operation but with generalized metastases, which first appeared three years after radical mastectomy. Another patient had local removal of a tumor which on gross examination was believed to be cellular fibroadenoma. Microscopically, its true nature was appreciated. Recurrences developed six months later, and radical mastectomy was done. The patient finally died from generalized metastases, the entire course of the disease having covered about two years.

The average age of these patients was 36 years, which was some ten years less than that of patients with adenosarcoma, with variations between 26 and 48 years. The average duration of symptoms was four and nine-tenths months.

LYMPHOBLASTOMA

Lymphoblastoma as the designation of a group includes lymphosarcoma, leukemic tumors, chloroma and Hodgkin's disease. All are rare in the breast, but lymphosarcoma is perhaps the most frequent. There are three general types: (1) that in which the process is localized to the breast; (2) that in which the first evidence of the disease appears in the breast and is later found to be part of a generalized process, and (3) that in which the breast involvement is but one manifestation of a systemic disease.

Lymphosarcoma.—Lymphosarcoma begins as a small tumor which enlarges rapidly and often produces symptoms and signs suggestive of carcinoma, so that radical mastectomy has been done because that type of neoplasm has been diagnosed. When lymphosarcoma is localized to the breast, the diagnosis can usually be made only after microscopic study. There may be single or multiple nodules, and the disease is sometimes bilateral. The axillary nodes are usually involved. Cases in which

23. Gross, S. D.: System of Surgery, Philadelphia, Henry C. Lea's Son & Co., 1882, p. 974.

it was associated with pregnancy have been reported by Elsberg²⁴ and by Schleiter and Bruecken.²⁵ There is no particular age distribution.

Grossly, there is usually a fairly well circumscribed, moderately firm nodule having a grayish white or pinkish gray homogeneous glistening cut surface. Occasionally, the disease is less well localized, and the general structure of the breast is preserved near the periphery of the lesion, where the lobules are enlarged and accentuated. Microscopically,

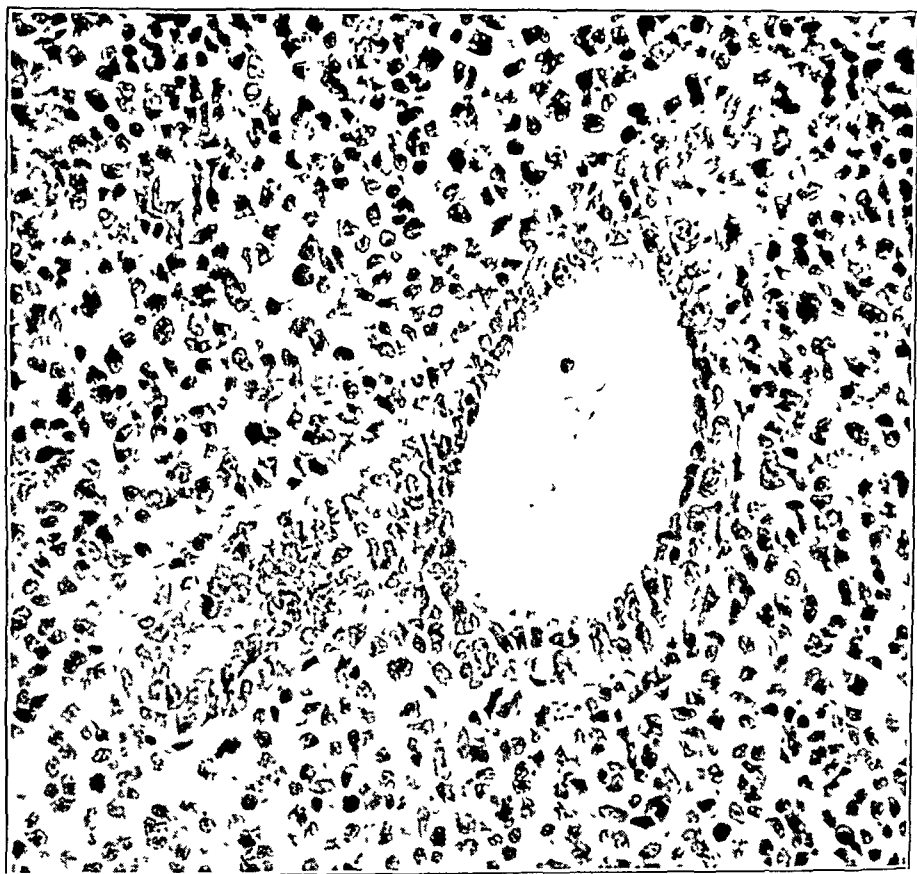


Fig. 12 (case 22).—Lymphosarcoma. The cells are evenly and uniformly distributed and approach the size of reticulum cells. An incorporated duct is present. The irregularity in cell shape is the result of shrinkage during fixation.

either the reticulum cell or the lymphocytic type may be found. The cells infiltrate the tissue diffusely and are closely packed near the center of the mass, where there may be only atrophic remnants or a complete absence of mammary structures (fig. 12). In the outer zones they are

24. Elsberg, C. A.: Multiple Lymphosarcoma of Both Breasts, *Ann Surg.* 60: 767, 1914.

25. Schleiter, H. G., and Bruecken, A. J.: Lymphosarcoma Involving Both Breasts, *Atlantic M. J.* 29:693, 1926

more scattered and are often confined chiefly to incompletely replaced lobules.

The origin of these cells is still uncertain. Since lymphocytes are not found in the normal breast, one explanation offered is that they appear in association with chronic cystic mastitis or some inflammatory process and later undergo malignant proliferation. Another theory is that the tumor arises in outlying glands and extends into the substance of the breast so that at the time of examination the mammary gland seems to be the primary site.

The treatment is irradiation or surgical removal or a combination of both. When the disease is recognized, radiotherapy is perhaps the method of choice, although there are examples of good results following surgical excision of localized lymphosarcoma of other regions. In any event, when operation is the primary method chosen, the axilla also should be removed, and it may be advantageous to follow such a procedure with a course of radiotherapy. Generally speaking, the course is rapidly fatal, although a few examples of long survival are recorded: Schreiner and Thibaudeau reported a survival of four years and nine months; Harrington and Miller, one of six years.

Hodgkin's Disease.—Hodgkin's disease appears rarely, if at all, in the breast as a local disease. Kückens²⁶ mentioned the case of a girl of 17 with a lesion apparently restricted to the breast. Mastectomy was done on the basis of a diagnosis of cancer, and microscopic examination showed numerous eosinophils, leukocytes, plasma cells and typical Sternberg cells. He assumed that the disease had originated in the lower axillary nodes, with subsequent extension into the breast. The case of Middleton²⁷ also belonged to this category. Schultz²⁸ referred to 2 cases of Kaufmann in which the breast was involved in a generalized process. In 1 of these, however, eosinophils, Sternberg cells, necrosis and fibrosis were lacking in the breast lesion. He adds another example with involvement of cervical, axillary and mediastinal lymph nodes. The signs and symptoms are much the same as for lymphosarcoma, and diagnosis is possible only after histologic examination. Radiotherapy offers the only rational treatment.

Leukemic Tumors.—Leukemic tumors form a perplexing group of mammary neoplasms. Not infrequently such tumors have been removed

26. Kückens, H.: Ein lokales Lymphogranulom der Brust in Form eines Mammatumors, Beitr. z. path. Anat. u. z. allg. Path. **80**:135, 1928.

27. Middleton, W. S.: Some Clinical Caprices of Hodgkin's Disease, Ann. Int. Med. **11**:448, 1937.

28. Schultz, A.: Die Lymphogranulomatose der Brustdrüse, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1933, vol. 7, pt. 2, pp. 169-173.

because of a diagnosis of carcinoma or lymphosarcoma with the later discovery that the patient was suffering from leukemia. In the older reports, a satisfactory examination of the blood had not always been made prior to operation, so that it is impossible to say whether or not the breast represented the first manifestation of the disease other than from a clinical standpoint. Haram²⁹ reported a case, however, in which the blood film was normal when the breast tumor first appeared. Later, when the opposite breast was the seat of similar nodules, the blood

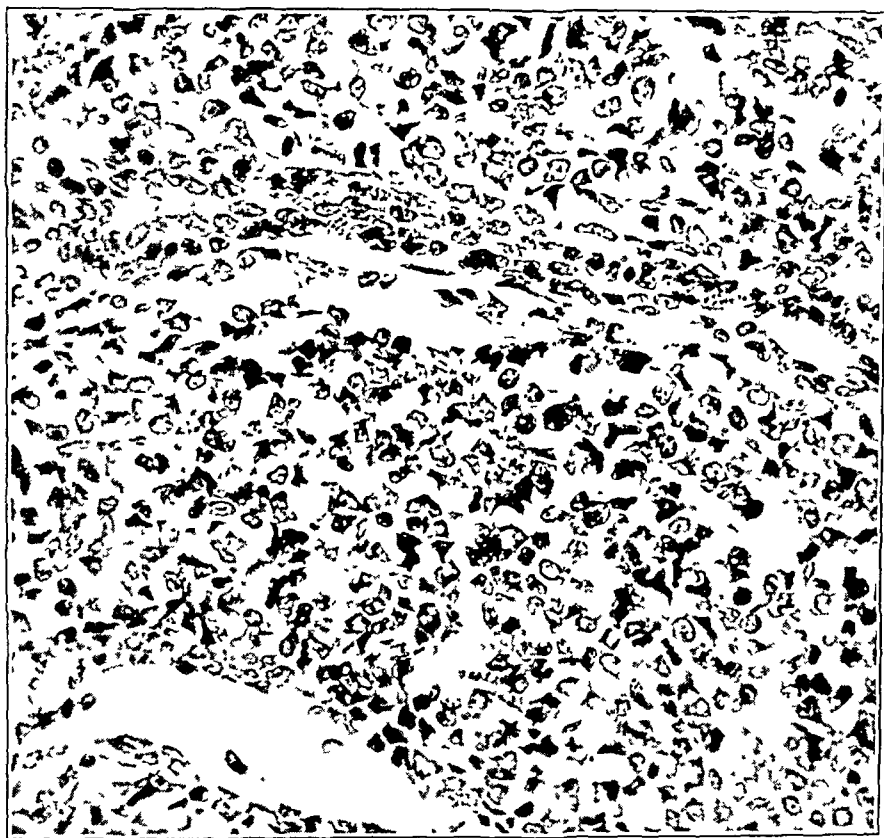


Fig. 13 (case 23).—Myeloid leukemia. The cells closely resemble those of lymphosarcoma. A compressed duct is present. The blood changes appeared after removal of the breast tumor.

showed a leukemic picture. The majority of the examples, though, have been associated with leukemic change in the blood. This may be either myeloid (fig. 13) or lymphoid (fig. 14) leukemia and is usually the acute type. Grossly and microscopically, the appearance of the nodules

29. Haram, B. J.: Lymphatic Leukemia with Bilateral Mammary Changes, *Lancet* 1:1277, 1937.

is similar to that of lymphosarcoma, and there are no differential characteristics. The course of the disease is one of rapid development and short duration.

Chloroma.—Chloroma embraces a group closely allied to the leukemic tumors. It appears most frequently in the short flat bones but is sometimes found in the breast, either as an isolated process or as a part of a more widespread condition. In almost all of the cases it is associated with leukemia; a notable exception is the case reported by Reid³⁰ in which up to the time of death the blood findings were relatively normal.

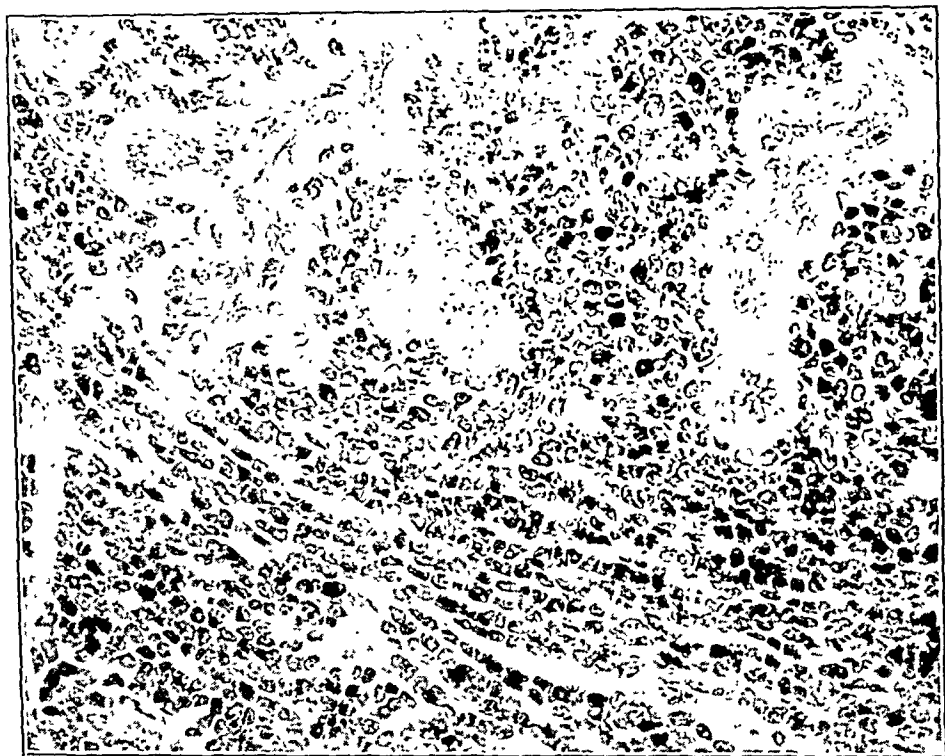


Fig. 14 (case 14).—Lymphatic leukemia. The tumor cells infiltrate the tissue evenly and diffusely, compressing and separating the included ducts.

The earlier writers on this subject expressed the belief that the blood changes were those of lymphatic leukemia, but more recent observers have found that the myeloid form is the more common. Kandel³¹ concluded that almost all of the cases belong to the myeloid group and that the older reports were probably in error because of the poorer histologic technics current at that time. The characteristic feature of the disease

30. Reid, M.: Ueber ein doppelseitiges myeloides Chlorom der Mamma, Beitr. z. klin. Chir. **95**:47, 1915.

31. Kandel, E. V.: Chloroma: Review of the Literature from 1926 to 1936 and Report of Three Cases, Arch. Int. Med. **59**:691 (April) 1937.

is, of course, the green color. Most of the cases terminate fatally within a few months, and even if the blood differential count is normal at the time of the first appearance of the tumor, subsequent examinations will reveal the true nature of the disease.

Two neoplasms observed in this laboratory have been diagnosed as lymphosarcoma and 2 as leukemia. There have been no examples of Hodgkin's disease or of chloroma. Diagnosis of 1 tumor classified as lymphosarcoma is uncertain, since the mass was removed incidentally from the breast of a patient who died after decompression for a brain tumor. No cerebral tissue was removed, and permission for an autopsy was not obtained. Therefore, the relation between the two lesions, if any, was never learned, and the classification has been made largely on histologic grounds. The other tumor appeared in a 54 year old woman who had radical mastectomy after a biopsy diagnosis of probable lymphosarcoma. Postoperative roentgen therapy was given, but the disease is of too recent occurrence to draw any conclusions as to the outcome. One of the leukemic neoplasms occurred in a 33 year old woman on whom local excision of a breast nodule believed to be benign lymphoma was done. Recurrence and involvement of the opposite breast led to bilateral radical mastectomy. Unfortunately, a blood count was not taken until after this operation; at this time typical lymphatic leukemia was found. The disease progressed to a fatal termination about six months after the first symptoms were noted. In the other patient, the first manifestation of the disease was a breast nodule; this was removed and thought to be lymphosarcoma. A short time later she returned to the hospital because of generalized symptoms, and a blood count then showed acute myeloid leukemia. Death ensued shortly thereafter; the entire course of the disease lasted only two months.

MALIGNANT HEMANGIOENDOTHELIOMA

Angioma, benign or malignant, occurring in the substance of the breast is unusual, and the number of authentic examples of the malignant form recorded in the literature is small. In the majority of instances a tumor of this type found in this region is cutaneous in derivation, and although the breast may have been involved by direct extension of the growth, the tumor should not be incorporated with those of true intramammary origin.

Since malignant angioma is infrequent, it is difficult to determine the actual proportion of malignant with respect to benign forms. There is a somewhat general belief that hemangioma of the breast is more prone to malignant change than hemangioma of other parts. To support this view

there is the observation of Menville and Bloodgood³² that in 11 per cent of the cases in their series the tumor was malignant. That no deductions can be drawn from such a result, however, is obvious as there were only 9 tumors diagnosed as angioma in a total of 3,000 breasts. For all cases of angioma, Geschickter and Keasbey³³ estimated that malignant characteristics were shown in less than 1 per cent.

Two types of benign angioma are found, the capillary and the cavernous. The former is the more common, and is difficult to differentiate from one of the malignant varieties which, seemingly benign from a histologic standpoint, ultimately metastasizes. Furthermore, hemangioma present for years as a benign growth may become malignant under the influence of trauma or recurrence.

Tumors diagnosed as malignant hemangioendothelioma can be divided into three general classes. In the first, the microscopic picture of both the primary and the metastatic lesion resembles that of simple angioma, and satisfactory criteria for early recognition are usually lacking. This benign appearance has led to the term "benign metastasizing hemangioma." The cases of Borrmann³⁴ and Ewing³⁵ belong to this class. The second type is more intermediate in character. The primary or initial tumor appears well differentiated and innocent, but the recurrent or the metastatic growth assumes a malignant aspect. Typical examples are those of Sherry,³⁶ Pulford³⁷ and Robinson and Castleman.³⁸ The third division includes those tumors recognizable as malignant from the beginning; they are illustrated in the cases of de Bary,³⁹ Da Costa⁴⁰ and Menville and Bloodgood.

32. Menville, J. G., and Bloodgood, J. C.: Subcutaneous Angiomas of the Breast, *Ann. Surg.* **97**:401, 1933.

33. Geschickter, C. F., and Keasbey, L. E.: Tumors of Blood Vessels, *Am. J. Cancer* **23**:568, 1935.

34. Borrmann, R.: Metastasenbildung bei histologisch gutartigen Geschwülsten (Fall von metastasierendem Angiom), *Beitr. z. path. Anat. u. z. allg. Path.* **40**:372, 1906.

35. Ewing, J.: *Neoplastic Diseases*, ed. 4, Philadelphia, W. B. Saunders Company, 1940, pp. 249-261 and 548-560.

36. Sherry, L. B.: Report of a Case of Hemangioma of the Breast, *West. J. Surg.* **42**:318, 1934.

37. Pulford, D. S., Jr.: Neoplasms of the Blood-Lymph-Vascular System with Special Reference to Endotheliomas, *Ann. Surg.* **82**:710, 1925.

38. Robinson, N. M., and Castleman, B.: Benign Metastasizing Hemangioma, *Ann. Surg.* **104**:453, 1936.

39. de Bary, E.: Ueber zwei Fälle von malignem Hämangioendotheliom, *Frankfurt. Ztschr. f. Path.* **46**:410, 1933.

40. Da Costa, J. C.: A Case of Endothelioma of the Mammary Gland, *Am. Med.* **5**:1024, 1903.

Incorporation of the first group in the malignant one has been criticized because of the possibility of a multicentric origin, a viewpoint hard to disprove. The presence, however, of an intermediate group of tumors which, originally considered innocuous, have produced recurrent or metastatic growths of undoubted malignant character seems strong evidence in favor of a single originating focus, with the reservation that surgical intervention may have been the stimulus inducing the malignant transformation. Another consideration, suggested by Borrmann, is that hemangioendothelioma is truly malignant from the beginning and that the histologic criteria are at fault. An illustrative example of this factor is found in a case in our series in which a tumor at first called capillary hemangioma showed on retrospect a few changes which might have suggested its true character. A somewhat analogous situation is found in certain cases of carcinoma of the thyroid in which the primary growth and lesions accepted as secondary deposits have revealed no microscopic cytologic changes suggesting malignancy.

Clinically, the diagnosis is difficult. Ordinarily the appearance is that of a rapidly enlarging unilateral tumor, which may be circumscribed or diffuse and irregular. Early the tumor tends to be soft and compressible, quickly assuming its former size when the pressure is released. After thrombosis and fibrosis have taken place, the consistency becomes more firm. Symptoms of pain, fluctuation and bruit are inconstant. The skin may or may not be involved and therefore is not always discolored, although when uninvolved, the dusky color of the tumor can sometimes be seen through it. The growth appears dark on transillumination and may attain a considerable size. A history of preexisting tumor of long duration is occasionally elicited.

The gross pathologic appearance is that of a soft spongy hemorrhagic mass, either circumscribed or infiltrating and often collapsing to some extent when sectioned. Microscopically, the picture varies from the well differentiated forms having the aspect of ordinary hemangioma to the highly cellular types showing little tendency to form recognizable vascular spaces. Foci of necrosis, hemorrhage and fibrosis are not infrequent. Remnants of breast structures may be found near the periphery.

The course is variable in its rapidity and largely dependent on the specific type concerned. The better differentiated tumors tend to grow slowly and metastasize late, while the more highly cellular forms often pursue a rapid course. Metastasis, when it occurs, is systemic; the axillary lymph nodes are rarely, if ever, involved. The prognosis is ostensibly poor since death resulted in 5 of 8 reported cases accepted

as clearly belonging to this group, and in 2 of the remainder the outcome was unknown or dubious. Both patients observed in this institution died.

Various methods of therapy have been advocated, but adequate surgical removal seems the best. Radiotherapy has been recommended and used but certainly without much success. In our experience, it has had no appreciable effect.

REPORT OF CASES

CASE 25.—A single white Jewish woman, aged 19, was admitted on July 30, 1935, to the outpatient department of the Presbyterian Hospital and Sloane Hospital for Women to the service of Dr. David C. Bull, with a slight blue discoloration of the skin just above the nipple of the right breast of three months' duration. A lump had appeared in this region during the last week before admission. Although at first painless, it had later become slightly tender. There was no history of trauma.

Physical examination revealed that the right breast was slightly larger than the left and that there was some retraction of the nipple. The areola was enlarged, and the upper half of it was faint blue. A firm smooth freely movable mass measuring about 3 by 2 by 1.5 cm. was felt beneath this area, and another similar mass was found immediately inferior to the nipple. The blue color was believed due to venous congestion, and the breast changes were considered those of chronic cystic mastitis. On this basis, the patient was given 120,000 rat units of estradiol benzoate in weekly doses of 10,000 units. By November, the lower mass had more than doubled its size, and the entire breast had enlarged. On December 11, at biopsy the neoplasm was called capillary hemangioma. During the ensuing four months there was no active therapy, and the lump continued slowly to increase in size. Quinine hydrochloride and ethyl carbamate (urethane) were then injected into the nodules from May 1936 to July 1936 with little resultant change. The breast, however, became hard and firm. Two weeks after the injections were stopped, the breast began to enlarge rapidly and became painful; a large dark purple area appeared over it. The patient was admitted to the hospital on September 18, and by this time the breast had attained dimensions of 18 by 15 by 10 cm. The nipple was flat, the entire breast was hard, and the skin was stretched and had a red, yellow, and purple mottled appearance. A review of the original biopsy specimen suggested the possibility of hemangioendothelioma. Roentgenograms of the chest revealed no abnormalities. Simple mastectomy was performed on September 30. Prior to operation an interesting finding had been a low blood platelet count; the count returned to normal after operation. In November the patient returned complaining of pain in the shoulders and the back. Shortly thereafter, a nodule was noted in the anterior abdominal wall. Roentgen examination now showed metastatic lesions in the left humerus, the right scapula and the upper lobe of the left lung. The thoracic and cervical vertebrae were normal. Later roentgenograms showed a suggestive lesion in the left scapula, but the spine, the skull, the pelvis and the femurs remained normal. On December 24, she suffered an attack of severe abdominal pain, and ecchymotic areas appeared on the lower extremities. The blood platelets again were found to be at a low

Data on Twenty-Four Cases of Sarcoma of the Breast

Case	Status of Patient *	Age, Years	Symptoms	Operation	Gross Appearance	Microscopic Appearance	Course
A. ADENOFIBROSARCOMA							
1	Married primipara	33	Tumor for 1 yr. with rapid growth in last 6 mo.; first appeared during lactation	Radical mastectomy	Encapsulated tumor measuring 9 by 7 cm.	Intracanalicular type; poorly cellular; entire mass showed sarcomatous change; few epithelial elements with no hyperplasia; nodes normal	Lost
2	Married	63	Injury followed by tumor which was present for 3½ yr. with more rapid growth in last year; pain	Radical mastectomy	Tumor measured 9 cm. in diameter; lobulated and traversed by clefts into which polypoid masses protruded	Intracanalicular type; sarcomatous change patchy in distribution; no epithelial hyperplasia; slight squamous metaplasia of epithelium; nodes normal	No evidence of disease after 136 mo.
3	Married	40	Lump for 1 mo.; no enlargement; slight tenderness	Local excision	Cyst filled with a polypoid mass measuring 1.5 by 3 cm.	Intracanalicular type; sarcomatous change patchy in distribution; no epithelial hyperplasia	No recurrence after 25 mo.
4	Married primipara	61	Tumor stationary in size for 42 yr.; trauma followed by enlargement 1 mo. before admission	Local excision	Tumor measured 5 cm. in diameter; remnants of fibroadenoma along one side containing foci of calcification	An intracanalicular fibroadenoma with a sarcomatous change in one part; epithelial elements lacking in cellular portion; invasion of adjacent fat	No recurrence after 18 mo.
5	Married	45	Tumor for 1½ yr.	Radical mastectomy	Encapsulated tumor measuring 9 by 12 cm.; cystic	Type of fibroadenoma uncertain; highly cellular; sarcomatous change diffuse; perithelial appearance resulting from necrosis; no epithelial hyperplasia; nodes normal	Lost
6	Single	48	Enlargement and tenderness of the breast for 8 mo.	Radical mastectomy	Cystic tumor measuring 11 by 13 by 16 cm.; excrescences protruding into cysts; some skin fixation	Intracanalicular type; poorly cellular with a diffuse sarcomatous change; no epithelial hyperplasia; nodes normal	Died from pulmonary embolus 11 days after operation; autopsy showed no spread of tumor
7	Married nullipara	52	Enlargement of breast for 6 mo. with more rapid growth in last 2 mo.; intermittent pain	Simple mastectomy	Tumor weighed 10 lb. (4.5 Kg.); cut surface nodular and cystic	Type of fibroadenoma undetermined; poorly cellular; sarcomatous change uniform throughout; no epithelial hyperplasia	No evidence of disease after 19 yr.
8	Single	53	Lump developed after a blow; slow enlargement for 3¼ yr.; rapid enlargement for 6 mo.	Simple mastectomy	Tumor measured 6 by 7 by 9 cm.; clefts and cysts with polypoid masses protruding into them; skin adherent	Fibroadenoma of mixed type; poorly cellular; diffuse sarcomatous change; moderate associated epithelial hyperplasia	Died 13 yr. after operation without evidence of recurrence
9	Married nullipara	39	Enlargement of breast for 6 mo.; pain for 1 mo.	Simple mastectomy	Tumor weighed 6½ lb. (3 Kg.); traversed by numerous clefts into which polypoid masses protruded	Fibroadenoma of mixed type; moderately cellular; sarcomatous change uniform throughout; considerable epithelial hyperplasia	No evidence of disease after 8 yr.
10	Single	60	Lump for 6 mo. with steady increase in size; slight pain	Radical mastectomy	Cystic tumor measuring 8 by 10 cm.; skin adherent in places; deposits of calcium	Intracanalicular type; highly cellular with diffuse sarcomatous changes throughout; few epithelial elements; nodes normal	Died 4 yr. after operation from cardiac complications without evidence of

11	Married	61	Lump for 1½ yr.; rapid growth for last 5 mo.; slight associated pain	Radical mastectomy	Tumor weighed 5,900 Gm.; attached to skin; superficial veins dilated; cut surface firm, whorled and nodular	Intracanalicular type; moderately cellular; sarcomatous change uniform throughout; some squamous metaplasia of epithelium	?
12†	40	Lump for 2 yr. with rapid growth for 1 mo.; skin ulcerated	Simple mastectomy	Tumor the size of a grapefruit and adherent to skin	Intracanalicular type; moderately cellular; sarcomatous change uniform throughout; some squamous metaplasia of epithelium	No recurrence after 8 yr.
13‡	Married	38	Lump for 2 yr.	Radical mastectomy	Circumscribed, firm tumor measuring 4 cm. in diameter traversed by a few clefts	Intracanalicular type; moderately cellular; sarcomatous change diffuse; invasion of adjacent fat; no epithelial hyperplasia; nodes normal	Lost
14§	Married quintipara	39	Nodule for 2 yr. with slow increase in size; rapid enlargement in last 2 mo.; some pain	Simple mastectomy	Encapsulated tumor measuring 10 cm. in diameter; cystic	Apparently pericanalicular type; moderately cellular; sarcomatous change diffuse; epithelial elements widely scattered; foci of cartilaginous metaplasia; cysts a result of necrosis	No recurrence after 6 yr.
15	Married nullipara	34	Lump for 4 yr. with slow increase in size	Local excision	Tumor measured 3 by 1 by 5 cm.; remnants of fibroadenoma at one end; part cystic with polypoid strands projecting into this portion	Hyalinized intracanalicular fibroadenoma with sarcomatous parts; areas with perivascular arrangement; foci of cartilage; squamous metaplasia of epithelium	Lost
16	38	Lump growing rapidly for 9 mo.; pain	Local excision (?)	Tumor measured 7 by 10 cm.; contained a central blood-filled cyst	Well differentiated fibrosarcoma; no epithelial elements	Lost
17	Single	35	Lump with slow increase in size for 11 mo.; some pain; skin red for 1 mo.	Radical mastectomy	Circumscribed, firm tumor measuring 3.5 by 3.5 cm.	Poorly differentiated fibrosarcoma; tumor giant cells present; no epithelial elements; nodes normal	No recurrence after 11 yr.
18	Single	48	Lump for 3 days	Local excision	Firm, circumscribed mass measuring 2 by 2 by 3 cm.	Well differentiated fibrosarcoma; focus of osteoid tissue near center; some invasion of surrounding breast; incorporated, atrophic ducts at periphery	No evidence of the disease after 6 yr.
19	Single	30	Lump with steady increase in size for 4 mo.	Radical mastectomy	Moderately soft, circumscribed tumor measuring 3.5 by 4.5 cm.; no adherence to skin or peritonal fascia	Well differentiated; scattered tumor giant cells; a few incorporated ducts at periphery; nodes normal	Local recurrence and distant subcutaneous metastases after 3 yr.; skin nodule showed similar well differentiated growth; patient living after 6 yr. with multiple metastases

* All these patients were women.

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|| Used by permission of Drs. J. C. Ehrlich and Chester Brown, New York.

¶ Used by permission of Drs. T. N. Goodson and A. O. Severance, San Antonio, Texas.

Used by permission of Dr. S. H. Polayes, New York (Leukemic Tumors of the Breast Mistaken for Lymphosarcoma, Am. J. M. Sc. 143: 518, 1912).

** Previously reported by G. A. McWilliams and F. M. Hanes.

Case	Status of Patient	Age, Years	Symptoms	Operation	Gross Appearance	Microscopic Appearance	Course
20	Married	36	Lump for 1 wk.; patient 3 mo. pregnant	Local excision as lesion was considered a highly cellular fibroadenoma on gross examination	Resilient, ovoid, apparently encapsulated tumor measuring 4 cm. in diameter	Original tumor cells medium sized, rounded or polygonal; little evidence of fibroblastic nature; in recurrence some cells spindle shaped and associated with small amount of collagen; many giant cells; axillary nodes normal	Recurred after 6 mo.; radical mastectomy; died 18 mo. later from metastases to lungs, left femur, pancreas and colon
C. LYMPHOSARCOMA							
21	Married primipara	22	Incidental mass in breast; admitted for symptoms of a brain tumor	Tumor excised after death	Circumscribed, soft tumor measuring 5.5 cm. in diameter	Medium-sized fairly regular cells arranged in diffuse fashion and supported by a fine reticulin network; some adult lymphocytes at periphery	Patient died after decompensation for brain tumor; no tissue removed; no autopsy; relation between two lesions uncertain
22	51	Lump for 3 wk.	Radical mastectomy after biopsy	?	Diffuse infiltration of regular medium-sized round cells; cells smaller at periphery and closely resembled adult lymphocytes; no axillary nodes isolated	Postoperative roentgen examination; patient symptom-free after 4 mo.
D. LEUKEMIA							
23#	25	Lump of uncertain duration	Local excision	Circumscribed ovoid tumor measuring 2.6 cm. in diameter	Medium-sized regular round cells arranged diffusely; some incorporated and atrophic ducts	Lesion thought to be lymphosarcoma; generalized symptoms developed 3 wk. after operation; re-admitted 3 mo. later and a blood count then showed acute myeloid leukemia (white blood count = 30,700 with 80% myelocytes); died shortly thereafter
24**	Married primipara	33	Lump for 2 wk.	Local excision—diagnosis: benign lymphoma; recurrence and involvement of opposite breast—bilateral mastectomy	Original tumor circumscribed, firm, pale and homogeneous; it measured 3 cm. in diameter; recurrent nodules similar	Numerous small round cells slightly larger than adult lymphocytes; infiltration most dense in lobules; axillary nodes involved	No blood count until after second operation; white blood count then 117,000 with 95% lymphocytes; died about 6 mo. after appearance of first symptoms

level (51,000). The abdominal symptoms were believed to be due to hemorrhage, as she soon passed into a state of shock. She died the following day. The entire course of the disease was thus about twenty-one months. Radiotherapy was given to the shoulders and the abdominal mass without appreciable benefit.

Biopsy (fig. 15) showed numerous variously sized anastomosing vascular spaces lined by a single layer of fairly uniform medium-sized endothelial cells. Some of the spaces contained blood; others were empty. The vessel walls were composed of a thin layer of hyalinized fibrous tissue. Although the lesion was



Fig. 15 (case 25).—Malignant hemangioendothelioma. The original biopsy specimen, showing the resemblance of the tumor to capillary hemangioma. There is little to suggest its malignant nature.

fairly well circumscribed, there was extension into the surrounding fat in one place.

The breast on removal weighed 1,647 Gm. When sectioned, it contained more than a liter of clotted and unclotted blood. Grossly, the cut surface appeared as a delicate spongy meshwork of numerous thin-walled large and small cavities.

There was a striking change from the findings of the original biopsy. Numerous irregular spaces were seen lined by large cells several layers thick so that sometimes the clefts were almost completely filled (fig. 16). The individual cell was

large, somewhat irregular, hyperchromatic and elongated with a deep-stained oval nucleus which sometimes contained one or more prominent nucleoli. Mitoses averaged about 1 per high power field. In the more cellular and compact areas, the cells had a roughly polygonal shape. Occasional foci were noted where the tumor resembled the biopsy specimen. There were extensive infiltration and almost complete replacement of the breast tissue. The vessels had anastomosed widely and often formed fairly extensive pools and lakes.

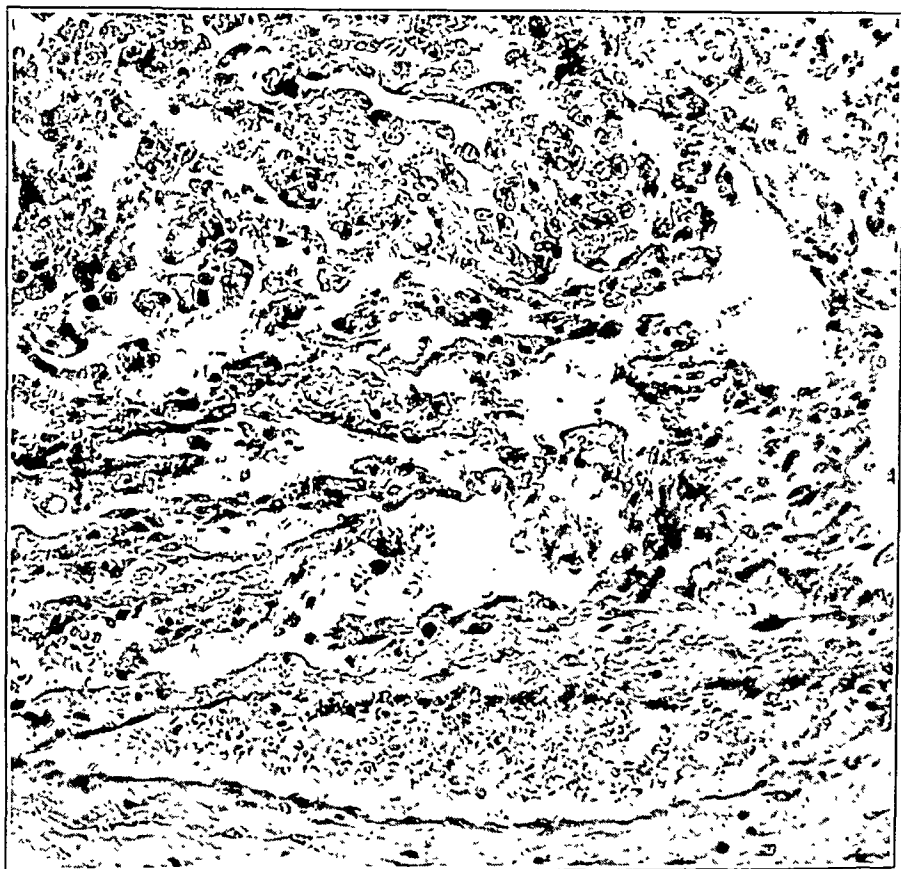


Fig. 16 (case 25).—Malignant hemangioendothelioma. The appearance of the lesion after amputation is shown. The tumor is now more cellular, and the cells lining the anastomosing vessels are piled-up, large and irregular.

CASE 26.⁴¹—A white woman, a widow 65 years of age, was admitted to the Memorial Hospital, Worcester, Mass., with a lump in the right breast. The symptoms had begun two weeks before with a stinging sensation in this breast followed soon after by the appearance of the nodule, rapid enlargement of the entire structure and purple discoloration of the overlying skin. There was some associated pain.

41. Used with the permission of Drs. Walter C. Seelye and James P. Beck, Worcester, Mass.

Physical examination revealed a mass the size of a golf ball 2 inches (5 cm.) lateral to the nipple with elevation of the overlying skin. The skin over the mass had a reddish purple hue, while the surrounding skin was slightly discolored and had a faint pigskin appearance. On palpation a mass about half the size of a grapefruit was felt in the substance of the breast in the vicinity of the elevated area. Roentgenograms of the chest revealed no abnormalities.

Radical mastectomy was performed, and one month later recurrent lesions developed in the scar. Roentgenograms now showed metastatic lesions in the lungs. Treatment of the recurrence and the metastases by irradiation had no effect. The patient became rapidly worse, and death occurred about two months after the onset of symptoms.

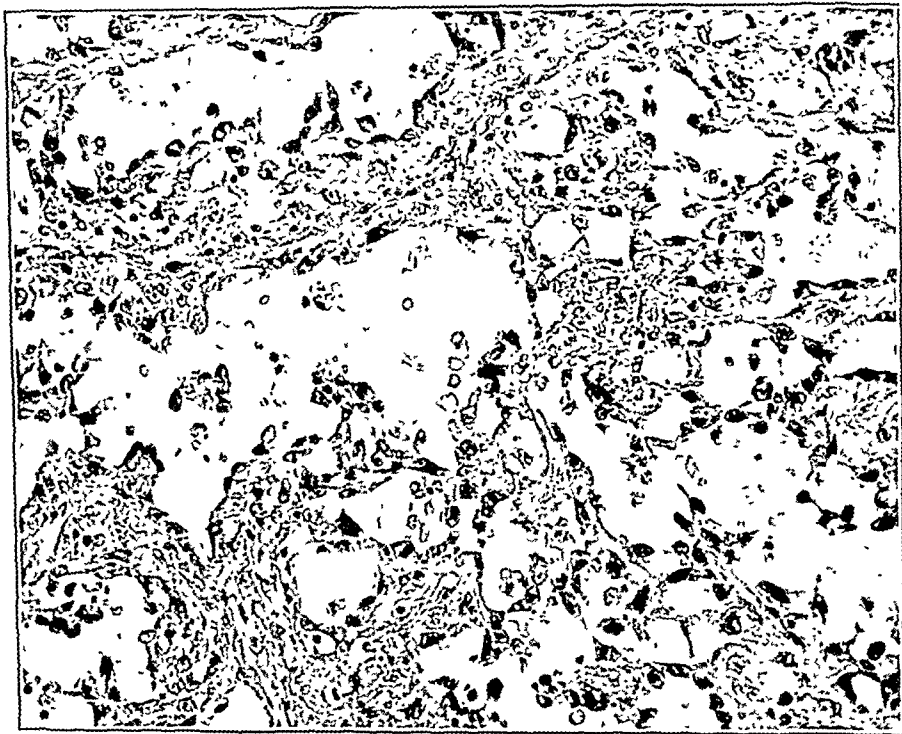


Fig. 17 (case 26).—Malignant hemangioendothelioma. The numerous, irregular anastomosing blood vessels are lined by large hyperchromatic cells which are sometimes piled up. Similar cells are found in the stroma.

Gross examination of the breast showed a large semifirm mass in the upper outer quadrant with elevation and thinning of the overlying skin. The nipple was retracted, and the skin over the entire outer half was blue. The tumor measured about 8 by 5 cm. Its cut surface was grayish white and semitranslucent and contained numerous small yellow opaque foci and areas of hemorrhage. Near the center was an irregular cavity filled with clotted blood.

Microscopically the breast was almost entirely replaced by large elongated hyperchromatic tumor cells arranged in indefinite vascular structures (fig. 17). The cells lining the channels varied from one to several layers thick. Some of the clefts contained a small amount of blood. The vessels were supported by a small amount of fibrous stroma, which was infiltrated by the tumor cells. Mitoses

averaged 2 to 5 per high power field. Foci of necrosis were present, and only a few mammary ducts remained. The overlying skin was ulcerated and intimately adherent to the growth. The axillary lymph nodes were normal.

LIPOSARCOMA AND MYOSARCOMA

Lifvendahl⁴² and Fox reported examples of liposarcoma appearing in the female mammary gland. Neal recorded a similar tumor occurring in the male breast. The relation to lipoma is uncertain.

Dretzka⁴³ described a breast tumor thought to be leiomyosarcoma. Bérard, Martin and Henry⁴⁴ observed a tumor which was called myosarcoma, and it seems likely that this neoplasm was of smooth muscle derivation. Isidor⁴⁵ mentioned a malignant tumor diagnosed as leiomyoma and believed to have arisen from the wall of a small artery. Neal found leiomyosarcoma involving the male breast. This diagnosis should be made on the presence of myofibrils and not on any superficial resemblance to muscle fibers.

Sailer observed what was undoubtedly rhabdomyosarcoma in the substance of the breast, and no connection with the pectoral muscles could be demonstrated. Leroux and Chaton⁴⁶ and Billroth noted striated muscle fibers in breast tumors. The source of this tissue is undetermined; perhaps these tumors represent teratomatous growths.

There are too few of these cases from which to draw conclusions other than that they seem to exhibit a rather high degree of malignancy. The clinical findings are much the same as for fibrosarcoma, and the differentiation can be made only by histologic means.

There have been no examples of these neoplasms observed in this laboratory.

MIXED TUMOR

The term "mixed tumor" has been used not specifically to limit but to simplify the discussion of the mammary neoplasm which contains two or more different tissues. We do not mean to convey the idea that every such growth should be designated simply as a mixed tumor; whenever possible, it should be classified according to the probable manner

42. Lifvendahl, R. A.: *Liposarcoma of the Mammary Gland*, Surg., Gynec. & Obst. **50**:81, 1930.

43. Dretzka, L.: *An Unusual Recurrent Mammary Tumor, with Pathological Opinions*, Am. J. Surg. **7**:693, 1929.

44. Bérard, L.; Martin, J. F., and Henry, M.: *A propos d'un cas de myosarcome mammaire*, Lyon chir. **34**:602, 1937.

45. Isidor, P.: *Essai d'étude critique des sarcomes du sein*, Gynécologie **33**:382, 1934.

46. Leroux, R., and Chaton, M.: *Dysembryome complexe de la glande mammaire*, Bull. Assoc. franç. p. l'étude du cancer **22**:80, 1933.

of its development. A malignant tumor of this nature is found both with and without malignant epithelial elements. Carcinosarcoma constitutes the first type, while malignant teratoma and fibrosarcoma or adenofibrosarcoma with osteoid or cartilaginous metaplasia belong to the second.

Cases of mammary neoplasm with foci of bone or cartilage or both have occasionally been recorded in the literature. Apparently the first reported was that of Bonet.⁴⁷ In 1937, Raso⁴⁸ was able to collect 74 cases and to add 1 of his own.

The source of the osteoid and cartilaginous elements has long been a subject of debate. Two explanations have been offered: (1) the theory of embryonic inclusion and (2) the theory of metaplasia.

The first view, in accordance with Cohnheim's theory, has been advocated by St. Arnold,^{48a} Wilms,⁴⁹ Lecène,⁵⁰ Hueter and Karrenstein,⁵¹ Dyke⁵² and others. St. Arnold suggested that a mixed tumor is a product of aberrant blastomeric inclusions from the developing thoracic skeleton and specifically from the region of the clavicle. This idea is dependent entirely on the concept of the specificity of the germ layers, a belief no longer considered tenable. Another view is that a mixed tumor is a result of misplacement of embryonic totipotent cells, a true teratoma. This possibility was demonstrated by the observance of teeth and a dental process in a mammary tumor by McIver⁵³ and of rudimentary hair follicles in another by Gioia and Bianchi,⁵⁴ structures which can be explained satisfactorily in no other way. Thus, malignant and one-sided deviation of one of the elements in such a tumor could lead to sarcoma or to carcinoma in which other structures would be found.

47. Bonet, T.: *Mammæ osseæ in virgine cum pectoris hydrope*, in *Sepulchretum sive anatomia practica ex cadaveribus morbo denatis*, Geneva, Cramer & Perachon, 1700, vol. 2, p. 522.

48. Raso, M.: *I Chondroosteomi e i condroosteosarcoma della mammella umana*, *Pathologica* **29**:229, 1937.

48a. St. Arnold: *Ueber einem knorpel- und knochenhaltigen Tumor der Brustdrüse*, *Virchows Arch. f. path. Anat.* **148**:449, 1897.

49. Wilms, M.: *Mischgeschwülste der Brustdrüse*, in *Die Mischgeschwülste*, Leipzig, A. Georgi, 1902, vol. 3, p. 169.

50. Lecène, P.: *Les tumeurs mixtes du sein*, *Rev. de chir.*, Paris **33**:434, 1906.

51. Hueter, C., and Karrenstein: *Eine Mischgeschwulst (Osteoidsarkom) der weiblichen Milchdrüse*, *Virchows Arch. f. path. Anat.* **183**:495, 1906.

52. Dyke, S. C.: *A Bony Tumour of the Breast*, *Brit. J. Surg.* **14**:323, 1926.

53. McIver, A. M.: *Teratoid Mixed Tumors of the Breast*, *Ann. Surg.* **77**:354, 1923.

54. Gioia, T., and Bianchi, A. E.: *Tumor mixto de la glándula mamaria en el hombre*, *Bol. y trab. Soc. de cir. de Buenos Aires* **14**:146, 1930.

Kreibig⁵⁵ reported a neoplasm containing foci of carcinoma, sarcoma, cartilage and osteoid tissue. In addition, a small fibroma and a hemangioma were associated, and he considered the lesion a malignant hamartoma. As a general rule, however, it seems unnecessary to explain the vast majority of these tumors on the basis of teratoma, and this possibility should be reserved for those explainable by no other means.

The metaplastic theory offers by far the best solution of the problem and has been supported by Stilling,⁵⁶ von Hacker,⁵⁷ Sehrt,⁵⁸ Deaver and McFarland, Thinnies,⁵⁹ Fry,⁶⁰ Ewing and Tudhope.⁶¹ The number of its exponents has increased greatly in recent years so that it is now the generally accepted explanation.

There are several reasons why this hypothesis seems more likely to be correct. It is not unusual to find definite stages of transition between the fibrous tissue of a tumor and its cartilaginous or osseous foci, an observation which formed the principal basis for the acceptance of the theory by the earlier writers. The frequent occurrence of bone or cartilage-containing tumors in the breasts of dogs is suggestive in that it seems somewhat far fetched to suppose that these animals are so much more prone to embryonic rests than human beings. The occasional presence of these elements in transplanted tumors of animals has been perhaps the most convincing evidence. Haagensen and Prime⁶² have several times noted the development of such tissues in the stroma of transplanted carcinomas of mice at the Cancer Research Laboratories of Columbia University. Further transplantations of these tumors, presumably not including the cartilaginous or osseous portions, have resulted in the sporadic appearance of these tissues. Foulds⁶³ obtained similar results with transplanted adenocarcinoma of the oviduct of a domestic

55. Kreibig, W.: Zur Kenntnis seltener Geschwulstformen der weiblichen Brustdrüse, *Virchows Arch. f. path. Anat.* **256**:649, 1925.

56. Stilling, H.: Ueber Osteoidsarkome der weiblichen Brustdrüse, *Deutsche Ztschr. f. Chir.* **15**:247, 1881.

57. von Hacker, V. R.: Ueber das Vorkommen von Knorpel und Knochen in einer Geschwulst der weiblichen Brustdrüse, *Arch. f. klin. Chir.* **27**:614, 1881-1882.

58. Sehrt, E.: Beiträge zur Pathologie der Milchdrüse, *Beitr. z. klin. Chir.* **55**:575, 1907.

59. Thinnies, H.: Ueber einem Fall von Chondrosarkom der weiblichen Brustdrüse, *Virchows Arch. f. path. Anat.* **264**:150, 1927.

60. Fry, H. J. B.: Osteoclastoma (Myeloid Sarcoma) of the Human Female Breast, *J. Path. & Bact.* **30**:529, 1927.

61. Tudhope, G. R.: A Complex Malignant Mammary Tumour, *J. Path. & Bact.* **48**:409, 1939.

62. Haagensen, C. D., and Prime, F. C.: The Spontaneous and Transplantable Tumors of Small Laboratory Animals, unpublished data.

63. Foulds, L.: A Transplantable Carcinoma of a Domestic Fowl, with a Discussion of the Histogenesis of Mixed Tumours, *J. Path. & Bact.* **44**:1, 1937.

fowl. Dunning, Bullock and Curtis⁶⁴ were able to produce osteochondrosarcoma in the mammary glands of rats with the injection of a solution of 3,4-benzpyrene, and so it would seem that bone and cartilage can be produced by fibrous tissue provided the local environmental conditions are right. Another factor against the specificity of the germ layers and the necessity of invoking fetal rests to explain a mixture of tissues is the modern concept of the possibility of cartilage formation by epithelial cells.⁶⁵

Therefore, it is probable that the presence of cartilage and bone in mammary tumors can usually be considered a metaplastic process, although of course some of the more complex and bizarre forms may have a teratomatous origin. Accordingly, it may be assumed that in most instances the primary lesion is fibroblastic in nature and that the osseous or cartilaginous change occurs secondarily. In many of the reports of cases the statement is made that the tumor resembled fibrosarcoma at its periphery, while the other elements were confined chiefly to the more central portions. That fibrosarcoma is the primary change has been suggested also by Isidor. For this reason, it is more accurate to speak of these neoplasms as fibrosarcoma with osteoid or cartilaginous metaplasia than as osteoid sarcoma or chondrosarcoma.

The clinical behavior is much the same as that of fibrosarcoma. How often metastatic foci produce bone or cartilage is uncertain since satisfactory data for the determination of this feature are lacking. That these foci may do so on occasion is demonstrated by the observance of cartilage in a secondary lesion by Raso and of osteoid tissue in metastatic deposits by Stilling. A somewhat analogous situation is the sporadic production of cartilage by certain transplanted tumors.

In the interpretation of the second class of malignant mixed tumors, i. e., composed of both sarcomatous and carcinomatous parts, carcinosarcoma, the same problems arise. The degree to which cancer cells can assume a spindle shape has been appreciated only in recent years as a result of the study of transplanted carcinoma in animals. This has definitely demonstrated that the mere spindle cell character of tumor cells cannot be considered sufficient evidence that the neoplasm is sarcoma. Hence, it appears likely that in many of the older reports supposed carcinosarcoma was really pure carcinoma. The fact that many of them recurred or metastasized as carcinoma suggests this conclusion. To be certain of the presence of both tumor elements, there should be metastases of both types, a criterion which is seldom found.

64. Dunning, W. F.; Curtis, M. R., and Bullock, F. D.: The Respective Roles of Heredity and Somatic Mutation on the Origin of Malignancy, *Am. J. Cancer* 28:681, 1936.

65. Allen, A. C.: So-Called Mixed Tumors of the Mammary Gland of Dog and Man, *Arch. Path.* 29:589 (May) 1940.

True combined carcinoma and sarcoma develops in three possible ways;

1. It may be true teratoma, and a malignant transformation of both epithelial and mesodermal tissues could produce such a growth. This constitutes the combination tumor of Meyer.⁶⁶

2. It is believed that carcinoma may sometimes incite its stroma to a sarcomatous proliferation. In this way, the composition tumor of Meyer or the carcinoma sarcomatodes of Takano⁶⁷ results. The reverse possibility is also true, namely, that surrounding epithelial elements may be stimulated to malignant proliferation by preexisting sarcoma. The observance of a sarcomatous change in the stroma of transplanted carcinoma in animals by Apolant,⁶⁸ Haaland,⁶⁹ Russell⁷⁰ and Haagensen and Prime suggests this possible mode of development. Further, Russell was able to take such mixed tumors, transplant their separate components and obtain a pure growth of each type. The supposed development of carcinoma during the propagation of sarcoma was noted by Nicholson.⁷¹

3. The same irritant may lead to the simultaneous reaction of both tissues; this is indicated by the appearance of similar growths in irradiated skins and in the subcutaneous tissues of rats by the injection of a solution of 3,4-benzpyrene.⁶⁴ Likewise, carcinoma and sarcoma may develop at the same time in the breast but in different regions and by continued growth subsequently coalesce. This was termed collision tumor by Meyer, and reputed examples have been reported by Schlagenhauser,⁷² Kettle,⁷³ Kennedy and Case⁷⁴ and Curphy.⁷⁵

Three of our tumors contained osteoid or cartilaginous tissue. In all there were transition stages between the fibrous tissue component

66. Meyer, R.: Beitrag zur Verständigung über die Namengebung in der Geschwulstlehre, *Zentralbl. f. allg. Path. u. path. Anat.* **30**:291, 1919.

67. Takano, N.: Ueber das Carcinoma sarcomatodes der Mamma, *Arch. f. klin. Chir.* **103**:154, 1914.

68. Apolant, H.: Die epithelialen Geschwülste der Maus, *Arb. a. d. k. Inst. f. exper. Therap. zu Frankfurt a.M.* **1**:11, 1906.

69. Haaland, M.: Contributions to the Study of the Development of Sarcoma Under Experimental Conditions, *Scient. Rep. Imp. Cancer Research Fund* **3**:175, 1908.

70. Russell, B. R. G.: Sarcoma Development Occurring During the Propagation of a Hemorrhagic Adenocarcinoma of the Mamma of the Mouse, *J. Path. & Bact.* **14**:345, 1910.

71. Nicholson, G. W.: A Small Carcinoma in Association with a Transplanted Sarcoma in a Rat, *J. Path. & Bact.* **16**:518, 1911.

72. Schlagenhauser, A.: Carcinom und Riesenzellsarkom derselben Mamma, *Centralbl. f. allg. Path. u. path. Anat.* **17**:385, 1906.

73. Kettle, E. H.: Carcinoma and Sarcoma of the Breast, *Lancet* **2**:750, 1912.

74. Kennedy, J. W., and Case, E. A.: Sarcoma and Carcinoma of the Same Mammary Gland, *Proc. Path. Soc. Philadelphia* **18**:40, 1916.

75. Curphy, W. C.: Primary Spindle Cell Sarcoma Associated with a Primary Scirrhus Carcinoma, *J. Kansas M. Soc.* **36**:412, 1935.

and the cartilage or bone. The osteoid tissue was found near the center of a tumor which was unquestionably fibrosarcoma, while the 2 cartilage-containing neoplasms were adenosarcoma. One of the latter showed cartilage both in the actively growing part and in the remnants of old hyalinized fibroadenoma. Similar changes have been noted also in fibroadenoma. We were permitted to review the sections from another tumor (Bernhard⁷⁶); these showed more extensive formation of osteoid elements, but again there was unmistakable evidence in places that the tumor was fibrosarcoma with extensive metaplasia. Dr. M. N. Richter of the New York Post-Graduate Medical School and Hospital showed us a section of a tumor which histologically resembled true osteogenic sarcoma, and from this section alone it was impossible to differentiate it from one. Unfortunately, it was an old case, and we do not know what additional microscopic preparations from other parts of the tumor might have revealed.

There were 2 tumors which may have been carcinosarcoma. In both there were nests of malignant epithelial cells separated by extensive bands of spindle cells suggestive of sarcoma. In 1 of them, formation of cartilage also had taken place. Since it is not within the scope of this paper to include any tumor with malignant epithelial elements, a detailed discussion of these 2 tumors is omitted; they have been mentioned only to complete the series.

SUMMARY

Breast sarcoma has been reviewed, and the diverse forms have been separated into fairly well defined groups according to histogenesis. The advantage of such a division becomes apparent when the prognosis is considered.

Adenofibrosarcoma constitutes a rather specific type of breast tumor and represents a sarcomatous transformation of fibroadenoma. It is the most frequently encountered variety and is usually clinically benign. On the other hand, true fibrosarcoma arising from the ordinary connective tissue of the breast has the same malignant potentialities as similar tumors in other regions.

It is believed that the presence of cartilage or bone in a breast tumor is usually a result of metaplasia in fibrosarcoma or adenofibrosarcoma and does not necessarily imply a teratomatous origin.

Myosarcoma, liposarcoma, malignant hemangioendothelioma and lymphoblastoma are interesting but unusual neoplasms which generally pursue a relatively rapid and unfavorable course.

Other terms often employed in the discussion of mammary sarcoma merely confuse further an already complicated subject and serve no practical purpose.

76. Bernhard, W. G.: To be published.

ECHINOCOCCOSIS OF THE BREAST

REPORT OF A CASE

JORGE A. TAIANA, M.D.

Fellow of the Rockefeller Foundation

BOSTON

AND

CARLOS J. STARACE

House Officer of the Centro de Investigaciones Tisiológicas

BUENOS AIRES, ARGENTINA

Echinococcosis may be localized anywhere in the body, but the breast is a rare location. In 1923, Escudero¹ made a complete review of the publications of cases echinococcosis of the breast, and since then few cases have been reported. Roldán² reported 1 case; Bussalay,³ 1; Pasman and Mosto,⁴ 1; Chifflet and Ardao,⁵ 2, and Charlone and Sacco-Ferraro,⁶ 1. Canavero⁷ published the report of a case of echinococcosis alveolaris of the breast.

The diagnosis of echinococcosis was made before operation in a few cases; commonly the diagnosis was made after operation. When Casoni's test of the skin and the Ghedini complement fixation test are positive and eosinophilia is present or when a puncture of the tumor gives clear fluid, the diagnosis of echinococcosis is easily made. Until now there has been no information about roentgen diagnosis of echinococcosis of the breast.

REPORT OF CASE

Mrs. E. C., a white married woman 24 years old born in Argentina, was admitted to the Centro de Investigaciones Tisiológicas in November 1940 com-

From the Centro de Investigaciones Tisiológicas, Prof. R. Izzo, Director.

1. Escudero, P.: Bibliografía de la hidatidosis: VI. Hidatidosis de las mamas, *Actas y trab. d. segundo Cong. nac. de med. argent.* **1**:558, 1923.

2. Roldán, A.: Quistes hidáticos, *An. Fac. de med. de Montevideo* **10**:291, 1925.

3. Bussalay, E.: Voluminosa cisti di echinococco della mamella. Estirpazione. Guarigione, *Policlinico (sez. prat.)* **5**:1779, 1927.

4. Pasman, F. R., and Mosto, D.: Quiste hidatídico de mama, *Prensa méd. argent.* **16**:1545, 1930.

5. Chifflet, A., and Ardao, H.: Quiste hidático de seno, *An. Fac. de med. de Montevideo* **20**:365, 1935.

6. Charlone, R., and Sacco-Ferraro, L.: Quiste hidático de la mama, *Arch. urug. de med., cir. y especialid.* **10**:607, 1937.

7. Canavero, M.: Su di una rara localizzazione dell' echinococco alveolare alla ghiandola mammaria, *Ann. ital. di chir.* **10**:566, 1931.

plaining of a tumor in the left breast which had been observed approximately three months before and which had progressively increased in size until admission. She had had no pain and no loss of weight.

Past History.—She was born in Pergamino, Province of Buenos Aires, and had had two sons and four abortions.

Physical Examination.—Physical examination revealed a fairly well developed white woman in good general condition. The temperature was normal; the pulse rate was 75; the blood pressure was 130 systolic and 85 diastolic. There was a tumor in the upper external quadrant of the left breast. Its surface was smooth, and it was about 5 cm. in diameter. It was renitent and gave the impression of a solid tumor not adherent to either the skin or the pectoralis muscles. The skin above the tumor was normal, and no infiltration could be felt around it. The

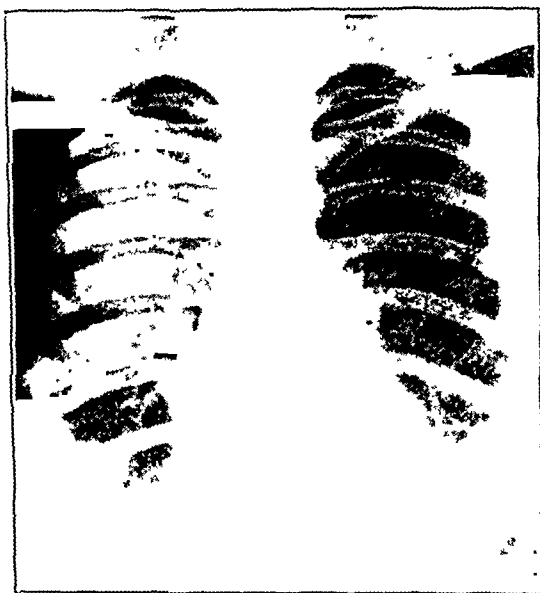


Fig. 1.—Roentgenogram showing the patient's normal chest.

examination was not painful, and it was easy to displace the tumor with the mammary gland. No lymph nodes were felt in the supraclavicular region or in the axilla. A roentgenogram showed a normal chest (fig. 1). The diagnosis was benign tumor of the breast (adenoma or adenofibroma), and operation was advised.

Operation.—On November 8, with local anesthesia induced with procaine hydrochloride, a radial incision was made in the breast, and an echinococcic cyst was found. An incision of 5 cm. was made in the adventitia, and the membrane of the parasite was completely removed. The inner surface of the adventitia was painted with a 10 per cent solution of formaldehyde; then the incision in the adventitia was closed with a continuous suture of catgut. The wound was closed in layers with catgut.

Progress.—The wound healed by primary intention (fig. 2). Two days later, examination of the blood showed 5,400 white cells and 7 per cent eosinophils. Seven days later, the complement fixation test was still negative.

Pathologic Report (Dr. L. Irigoyen).—The specimen was a cyst with whitish flexible walls which contained transparent fluid (fig. 3).

Microscopic Description: The wall of the cyst did not have any tissue structure. It consisted of two parts: the outer (cuticular) part, which was formed of



Fig. 2.—The scar seven days after operation.



Fig. 3.—The membrane of the parasite.

many layers, and the inner (germinative) part, which contained grains which, when enlarged, showed some scolices. The diagnosis was echinococcic cyst.

COMMENT

In our patient, who was born and grew up in a place where echinococcic cyst is common, the most important features were: a slow increase in the size of the tumor, a smooth surface and a great mobility.

The treatment in many cases has consisted of partial resection of the breast, including the parasite, the adventitia and portions of the mammary gland. It is not necessary to remove any part of the mammary gland unless there is severe chronic infected mastitis. We believe that the best procedure is the application of Posadas' technic⁸ performed in our case: complete evacuation of the parasite, dabbing the inner surface of the adventitia with solution of formaldehyde and complete closure of the wound.

8. Posadas, A.: Traitement des kystes hydatiques, *Rev. de chir.* **19**:374, 1899.

MOTILITY AND RESPONSE OF THE GREAT OMENTUM

I. FLUOROSCOPIC OBSERVATIONS ON OMENTAL ACTIVITY OF DOGS

ROBERT E. ROTHENBERG, M.D.

AND

PHILIP ROSENBLATT, M.D.

BROOKLYN

There have been innumerable speculations on the functions and activity of the great omentum. Theories have varied from that of Erisistratus,¹ who centuries ago claimed the structure had no function, to those of modern writers who speak of the "intelligence" of the omentum. And even today, a survey of the medical literature shows that many different opinions are held concerning the physiology of this structure.

Almost all students are informed that the omentum is the "great protector of the abdomen" which by some strange inherent power seeks out and tries to arrest trouble. However, extensive experience with abdominal operations for intraperitoneal suppuration has repeatedly demonstrated that the omentum is indeed capricious in its response to such calls of duty. The observations reported here are the first in a series of studies which will attempt to clarify the problem of omental activity and response. Additional experiments are being conducted to determine the extent of chemotactic and phagocytic response, secretory and absorptive function and the ability of omental grafts to survive.

It is a matter of common medical knowledge that the omentum is often found adherent to inflamed structures within the peritoneal cavity. In 1896, Stichler² introduced small nails into the peritoneal cavity of dogs and observed that they were walled off by the omentum. In 1899, Milran,³ after a series of experiments on various laboratory animals, concluded that the omentum was endowed with motility and that this motility was longitudinal, transverse and about the axis of the omentum itself.

While all writers on the subject agree that the great omentum has motility, they are divided into two schools concerning the mechanism

From the Departments of Research Surgery and Laboratories, Jewish Hospital.

1. Erisistratus, cited by Hertzler, A. E.: *The Peritoneum*, S. Louis, C. V. Mosby Company, 1919, vol. 1.

2. Stichler, cited by Siciliani.⁶

3. Milran, cited by Siciliani.⁶

of its ability to travel from place to place. The theory of intrinsic omental motility was most vigorously championed by Rutherford Morison,⁴ Saint and Dunelm⁵ and Siciliani.⁶ Morison spoke of the great omentum as the "policeman of the abdomen" that travels about with considerable activity and is attracted by some sort of information to neighborhoods in which mischief is brewing. He likened these movements to those of a jellyfish. Siciliani expressed the opinion that the omentum has active power of movement, and while he did not state what the origin of the motility is, he suggested that it may be due to its "histological structure and biological properties."

In 1906, Fisher⁷ expressed the opinion that the great omentum does not have intrinsic motility. Wilkie⁸ and Adams⁹ also opposed the concept of active omental motility and explained the excursions as being produced by peristalsis. Normally, the peristaltic movements of the small intestine keep the great omentum spread uniformly over the surface of the intestine. When local inflammation involves the peritoneal covering of a few coils of the small intestine, the movements of these coils are restrained. This inactivity of the intestine produces a quiescent area, and the great omentum is pushed by actively moving coils of intestine toward this quiescent region. When the omentum eventually comes in contact with the inflamed area, it becomes involved in the inflammatory process itself. The inflammation produces adhesions between the omentum and the bowel and thereby tends to limit the spread of the infection.

Except for the work of Florey, Walker and Carleton¹⁰ in 1926 and of Siciliani in 1932, little experimental investigation has been carried out in recent years that added to the knowledge of this subject. Indeed, Johnson¹¹ in 1930 stated that no one knows or has proved what the automotive power of the great omentum may be. However, in justice to Florey, Walker and Carleton, it should be said that they built up a strong case in favor of the theory of passive motility. Their experiments led them to believe that the movements of the great omentum in the cat, the rabbit and the mouse were purely passive.

4. Morison, R.: *An Introduction to Surgery*, Bristol, England, John Wright & Sons, 1910.

5. Saint, C. F. M., and Dunelm, M. S.: *Clin. J.* **44**:172, 1915.

6. Siciliani, G.: *Folia med.* **18**:949, 1932.

7. Fisher, T.: *Brit. M. J.* **2**:1329, 1911.

8. Wilkie, D. P. D.: *Brit. M. J.* **2**:1103, 1911.

9. Adams, S. E.: *Lancet* **1**:663, 1913.

10. Florey, H.; Walker, J. L., and Carleton, H. M.: *J. Path. & Bact.* **29**:97, 1926.

11. Draper, J. W., and Johnson, R. K.: *Tr. Am. Gastro-Enterol. A.* **33**:30, 1930.

According to these investigators, the factors involved are: (1) posture, (2) peristalsis and (3) diaphragmatic excursions.

In 1913, Adams observed omental movements fluoroscopically, but his work has been criticized because he used lead shots as opaque bodies. Saint and Dunelm expressed the belief that these lead shots added appreciable weight to the free border of the omentum and consequently inhibited its motility. Florey's work of direct observation of omental activity by means of windows in the wall of the abdomen is open to the criticism that artificial conditions prevailed which might have altered omental response.

EXPERIMENTAL DATA

Our studies were directed toward the observation of omental motility and response under conditions as near to normal as possible. Through high mid-epigastric incisions, various opaque bodies were sutured into the free border of the great omentum of 4 dogs. The high incision was chosen to avoid postoperative adhesions between the parietal peritoneum and the free portion of the omentum. Silver brain clips were buried with an inverting suture into the free edge of the omentum of 2 dogs; Michel clips were used for a third dog, and leaded glass thread was the material used for a fourth animal. All of these opaque bodies were so small and light that their size and weight could not possibly be appreciable factors in influencing motility or response of the great omentum.

EXPERIMENT 1.—The dog was a white female fox terrier, weighing 7 Kg. With the dog under anesthesia induced with the intravenous administration of soluble pentobarbital, a high mid-epigastric incision 4 cm. long was made, and the great omentum was brought out of the wound. The omentum was thin and semimembranous, measuring 15 cm. from the greater curvature of the stomach to its free edge on the right side and 12 cm. along the left border. An open Michel clip was buried in the lowermost dependent portion of the right side by means of an inverting black silk suture. Similarly, a closed Michel clip was sutured into a corresponding position on the left side. The great omentum was carefully replaced in the abdominal cavity, and the wound was closed in layers.

Three weeks later, the animal was examined under the fluoroscope in the supine position. Its legs were firmly held by two assistants, and within a few moments the animal lay quiet and passive. The clips were seen to move up and down with respirations, closely following the diaphragmatic excursions. The range of movement was approximately 1 cm. No lateral or axial movements were noted despite repeated observations extending over a period of about one-half hour. The dog was then given 1.5 cc. of a 1:2,000 solution of prostigmine methylsulfate intramuscularly. Several minutes later exceedingly active peristalsis was noted, evidenced by the rapid progression of gas bubbles within the bowel. At the height of peristaltic activity the left clip ascended and approached the right clip, which remained relatively immobile in the right upper quadrant of the abdomen. Five minutes later, the animal vomited and immediately thereafter was placed under the fluoroscope. No omental movement was seen. Shortly afterward, the dog defecated and was again viewed under the fluoroscope, but no omental excursions were made out.

Two weeks later, the experiments were repeated with exactly similar results. After the effect of the prostigmine methylsulfate was allowed to wear off, a sterile

5 cm., 22 gage needle was inserted into the right lower quadrant of the abdomen, at the level of the lowermost extent of the omentum on the opposite side of the abdomen. The right clip was located about 4 cm. above the level at which the needle was introduced. This point was chosen in order to see whether the right clip would descend or the left clip would move transversely in response to the irritation of the foreign body. No omental response, as indicated by a change of position, was noted over a period of some fifteen minutes despite manipulation of the needle in all directions (see illustration).



The clips are in the free border of the dog's great omentum, and the sterile needle has been introduced into the peritoneal cavity. A similar site was chosen for the inoculation of *B. coli*. This area is well within reach of the omentum

One month later, 0.5 cc. of a fresh virulent culture of *Bacillus coli* containing 6,000,000,000 organisms per cubic centimeter was injected into the peritoneal cavity of the right lower quadrant of the abdomen. Six hours later, the animal was observed under the fluoroscope, and the clips were seen to be in their former positions nowhere near the site of the implantation of bacteria. This procedure was repeated two weeks later when 1 cc. of a heavy suspension in a solution of sodium chloride of purulent material obtained from the lumen of a suppurating appendix was injected intraperitoneally into the right lower quadrant of the abdomen. *B. coli* was subsequently cultured from this suspension. Twenty-six

hours later, the animal was examined under the fluoroscope, but no change in omental position was observed.

Because of the failure of the omentum to respond to either the insertion of a needle or the implantations of bacteria, it was thought that adhesions might have formed after the original laparotomy, thus restraining all omental activity. Exploratory laparotomy was therefore performed through a left midrectus incision. No adhesions were found within the abdominal cavity, nor was there any evidence of previous peritonitis. The clips were located and found to be completely encapsulated. The free edge of the omentum was entirely mobile, and except for slight induration about the clips, there was no evidence that any changes had occurred as a result of the original operation for their insertion.

EXPERIMENT 2.—The dog was a black male mongrel and weighed 9.4 Kg. With the animal under anesthesia induced with the intravenous administration of soluble pentobarbital, a high midepigastic incision 4 cm. long was made, and the great omentum was brought out of the wound. It was moderately fatty, measuring 8.5 cm. from the greater curvature of the stomach downward to its free border along the right side, 6 cm. along the left side and 14 cm. in its midportion. Two strands of leaded glass silk were buried in the free edge of the midportion of the most dependent part, and one strand was buried in the right and left extremities of the omentum, respectively. The abdomen was closed in layers after the omentum had been carefully repositioned.

Three weeks later, the animal was examined under the fluoroscope. The leaded glass silk was seen to move up and down synchronously with respiration, within an excursion of approximately 1 cm. No lateral or axial movements were observed. After a period of study of about one-half hour, during which no changes in the type of omental mobility were perceived, the dog was given 1.5 cc. of a 1:2,000 solution of prostigmine methylsulfate by intramuscular injection. Ten minutes later, active intestinal peristalsis became clearly visible, and the right free border of the omentum was seen to approach the midline. The distance between the strands of silk decreased markedly. During the examination, the dog defecated, but this did not appear to influence the movements of the omentum.

Two weeks later, the procedure was repeated with similar results. When the effects of prostigmine methylsulfate had worn off, a sterile 5 cm., 22 gage needle was inserted into the peritoneal cavity in the left lower quadrant of the abdomen at the level of the lower border of the omentum. Despite manipulation of the needle in all directions, no omental movements were noted during a period of some fifteen minutes.

Three months later, 1.5 cc. of a fresh virulent culture of *B. coli* containing about 5,000,000,000 organisms was injected into the peritoneal cavity in the left lower quadrant of the abdomen. Fluoroscopic examination twenty-four hours later showed no change in the position of the leaded silk.

Exploratory laparotomy performed six weeks after the implantation of bacteria showed the omentum to be completely free of adhesions. The leaded silk was encapsulated by the omentum, which was only slightly thickened. At the site of the injection of *B. coli*, there were a few fine adhesions between the serosa of the sigmoid colon and the parietal peritoneum of the lateral wall of the abdomen.

EXPERIMENT 3.—The dog was a tan and white female mongrel and weighed 12.3 Kg. With the dog under anesthesia induced with the intravenous administration of soluble pentobarbital, a high midepigastic incision was made, and a rather

fatty omentum was delivered into the wound. Silver brain clips were buried in the free edges of the omentum in the right, left and central portions, which measured, respectively, 12, 7 and 14.5 cm. in length from the greater curvature of the stomach. The omentum was replaced, and the abdomen was closed in layers.

After three weeks, fluoroscopic maneuvers similar to those in experiments 1 and 2 were performed with identical results. The great omentum was seen to move only as the result of vigorous peristalsis induced by the injection of prostigmine methylsulfate.

Similarly, the injection of 5,000,000,000 virulent *B. coli* failed to produce any noticeable response within twenty-four hours. Exploratory laparotomy one month later showed slight induration of the omentum about the clips but no peritoneal or omental adhesions.

EXPERIMENT 4.—The dog was a brown female mongrel and weighed 10 Kg. With the dog under anesthesia induced with the intravenous administration of soluble pentobarbital, a high midépigastric incision 4 cm. long was made, and a slightly fatty omentum was brought out of the wound. Silver brain clips were buried in the right, left and central extremities of the omentum, 16, 10 and 17 cm., respectively, from the greater curvature of the stomach. The omentum was carefully repositied, and the abdomen was sutured in layers.

Three weeks later, fluoroscopic procedures similar to those in the other 3 experiments were conducted, and like observations were noted. Vomiting, defecation and the insertion of a sterile needle into the peritoneal cavity did not induce change in the position of the omentum. On the other hand, the vigorous peristalsis brought on by prostigmine methylsulfate produced definite lateral and longitudinal excursions of the omentum.

The injection of 5,000,000,000 virulent *B. coli* into the peritoneal cavity showed no evidence at fluoroscopy of having stimulated omental movement or change in position. Five weeks later, exploratory laparotomy was performed and revealed no omental adhesions. A few fine fibrous adhesions between the appendices epiploicae of the sigmoid flexure of the colon and the parietal peritoneum were found at the site of the previous inoculation of bacteria.

COMMENT

Normal conditions were simulated closely in all 4 experiments. The clips and the opaque thread buried in the omentum were light and small so that the factor of inertia was obviated. At subsequent laparotomy, the inflammatory reaction around the buried materials was found to be negligible. As no adhesions involving the great omentum developed, we were therefore assured that those movements which were seen were actually those of the unhampered omentum. The clips and the thread were clearly visible under the fluoroscope, and it was easy to follow their excursions.

In all instances, respiration caused longitudinal movement of the omentum over a distance of approximately 1 cm. These movements were synchronous with respiration, the omentum descending with inspiration and ascending with expiration. On repeated fluoroscopic

examination of the 4 animals in the resting state, no intrinsic lateral, longitudinal or axial omental movements other than those caused by respiration were seen.

The introduction of a needle at a site within easy reach of the omentum and its manipulation within the peritoneal cavity produced no response during a period of some fifteen minutes. This negative finding was particularly significant to us, for if the omentum was really endowed with active "intelligence," one might expect it to respond immediately to such a stimulus. This leads us to believe that the encapsulation of the foreign body which occurs after a few days is purely passive in character and is not dependent on any active intrinsic property of the omentum.

The physiologic processes of vomiting and defecation did not induce omental motility. On the other hand, hyperperistalsis induced by the injection of prostigmine methylsulfate resulted in definite lateral and longitudinal changes in the position of the omentum. These excursions measured anywhere from 3 to 6 cm. in extent. The conclusion to be drawn from these observations is that the omentum is moved passively by exaggerated peristaltic activity of the underlying coils of bowel. While vomiting and defecation are also concerned with peristalsis, in these processes the intestinal contractions are not vigorous enough to impart their effects to the overlying omentum.

The peritoneum was irritated by implanting large doses of virulent *B. coli* at a site within reach of the great omentum. Generalized peritonitis did not develop in any animal, even though the dose of organisms was greater than that reported by Coller, Ransom and Rife¹² as lethal for normal dogs. The peritoneum apparently handled the insult locally, for the omentum did not respond within an observation period of twenty-four hours. Fluoroscopic examination before and twenty-four hours after the implantation of bacteria revealed no changes in the position of the omentum. At subsequent laparotomy several weeks later, the omentum lay free within the peritoneal cavity and showed no evidence by adhesions or by changes in location of having taken part in the defense against the bacterial invasion. Adhesions of the bowel to the wall of the abdomen were present in 2 dogs at the sites of the implantation of bacteria. This suggests the conclusions that the peritoneum handles most insults locally and that perhaps the omentum becomes involved only by contiguity or by situations in which the peritoneum is overwhelmed and is unable to combat the infection alone.

12. Coller, F. A.; Ransom, H. K., and Rife, C. S.: Reactions of Peritoneum to Trauma and Infection: Further Experimental Studies, *Arch. Surg.* **39**:761 (Nov.) 1939.

SUMMARY AND CONCLUSIONS

The great omentum of the dog has no active intrinsic motile power. Slight longitudinal excursions of the omentum are caused by respiration. Vomiting and defecation do not produce changes in the position of the omentum. Hyperperistalsis produces marked longitudinal and lateral movements of the omentum. Movements of the great omentum are passive and are dependent on the activity of the underlying bowel. There is no immediate response of the omentum to the insertion of a foreign body into the peritoneal cavity. The peritoneum of the bowel and the wall of the abdomen handled the intraperitoneal injection of several billion virulent *B. coli* locally. Although the site of injection was within easy reach of the great omentum, it did not move to the vicinity, nor did it take part in localizing the process.

PREGANGLIONIC COMPONENTS OF THE FIRST THORACIC NERVE

THEIR ROLE IN THE SYMPATHETIC INNERVATION
OF THE UPPER EXTREMITY

ALBERT KUNTZ, M.D., PH.D.

AND

JOHN B. DILLON, M.S.

ST. LOUIS

Operative procedures designed to effect functional sympathetic denervation of the upper extremities have occupied the attention of surgeons and experimental investigators. Clinical reports of cases in which operations for sympathetic denervation of the upper extremity have been carried out in the treatment of peripheral vascular disease indicate a relatively high percentage of failure to obtain complete functional elimination of the vasomotor and sudomotor nerves. This is due in part to anatomic variations. On the other hand, some of the operative procedures which have been outlined are not based on complete knowledge of the anatomic relations of the nerves in question and are not sufficiently extensive to interrupt all the sympathetic pathways leading into the upper extremity.

The gray communicating rami through which sympathetic fibers join the brachial plexus are derived mainly from the cervicothoracic and the middle cervical sympathetic ganglions. These ganglions receive preganglionic fibers via the white communicating rami of the first and lower thoracic nerves. It does not follow, without further proof, that all these white rami convey preganglionic fibers which effect synaptic connections with ganglion cells the axons of which extend into the upper extremity. The results reported by various investigators have not led to the same conclusions regarding the sources of the preganglionic fibers involved in the sympathetic innervation of the upper extremity.

On the basis of the data obtained in a series of anatomic and physiologic experiments carried out on cats and dogs, Kuntz, Alexander and Furcolo¹ concluded that the white communicating rami of the first and lower thoracic nerves include preganglionic fibers which effect synaptic connections with ganglion cells involved in the sympathetic innervation of the upper extremity. Preganglionic components of the

From the departments of microanatomy and physiology of the St. Louis University School of Medicine.

1. Kuntz, A.; Alexander, W. F., and Furcolo, C. L.: Complete Sympathetic Denervation of the Upper Extremity, *Ann. Surg.* **107**:25-31, 1938.

first and lower thoracic nerves also extend upward in the cervical portion of the sympathetic trunk. According to their findings, axons of ganglion cells in the cervicothoracic (stellate) ganglion, which are synaptically related to preganglionic components of the first thoracic nerve, are relatively widely distributed in the upper extremity, particularly in the distal portions, both to the vascular musculature and to the sweat glands.

In a recent investigation of the sympathetic preganglionic outflow to the limbs of monkeys, Sheehan and Marrazzi² used the action potential records obtained from peripheral nerves on stimulation of the ventral nerve roots as criteria of the conduction of impulses through sympathetic fibers. On the basis of their findings, they reported that in the rhesus monkey the preganglionic outflow to the upper extremity is limited to the fourth to the eighth thoracic nerves inclusive, with the major outflow in the fifth, sixth and seventh. They found no evidence of preganglionic fibers to the upper extremity in the first, second or third thoracic nerves. Although they presented no new data bearing on the preganglionic sympathetic outflow to the upper extremity in cats and dogs, they expressed the opinion that the results of faradic stimulation of the ventral roots of the upper thoracic nerves reported by Kuntz, Alexander and Furcolo may have been vitiated by unobserved spread of the stimulating current.

In view of the importance of more exact knowledge regarding the distribution of the preganglionic components of the upper thoracic nerves, it has seemed desirable to carry out a further study with the aid of a technic which is not subject to the errors which may result whenever ventral nerve roots are stimulated directly. The photoelectric plethysmograph affords such a method since it provides a convenient means of recording changes in the amplitude of the volume pulse wave due to reflex vasoconstrictor stimulation, particularly in the distal segments of the digits. This apparatus and its application in investigations involving changes in the peripheral circulation have been amply described by Hertzman and Dillon.³

METHOD

In the present series of experiments, carried out on cats and rhesus monkeys, the volume pulse wave in the toe or the finger pads was recorded while the afferent stimulus (ice or faradic stimulation) was applied to one of the lower extremities. With the animals under anesthesia induced with soluble pentobarbital, records were taken before operation, after extirpation of the second and third

2. Sheehan, D., and Marrazzi, A. S.: Sympathetic Preganglionic Outflow to Limbs of Monkeys, *J. Neurophysiol.* **4**:68-79, 1941.

3. Hertzman, A. B., and Dillon, J. B.: Distinction Between Arterial, Venous and Flow Components in Photoelectric Plethysmography in Man, *Am. J. Physiol.* **130**:177-185, 1940.

thoracic segments of the sympathetic trunk, leaving the first thoracic nerve with its white communicating ramus and the cervicothoracic ganglion with its gray communicating rami intact, and after extirpation of the cervicothoracic ganglion in addition to the second and third thoracic segments of the sympathetic trunk. The records after operation were never taken on the day on which the operation was carried out but always after ample time had elapsed to permit of recovery from the effects of operative trauma or shock.

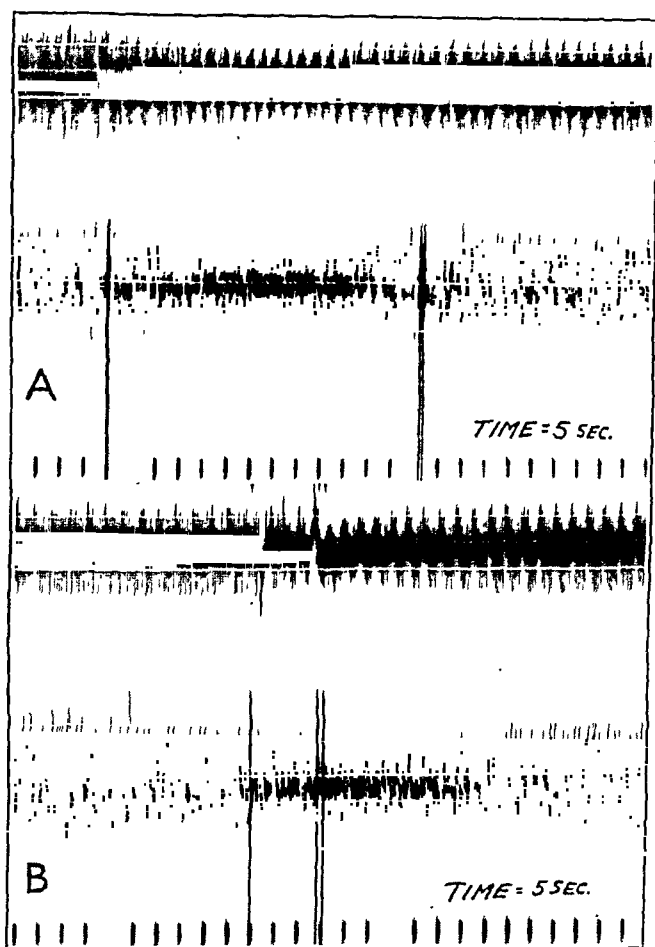


Fig. 1.—Photoelectric plethysmographic records from toe pads of the upper extremity of a cat under anesthesia induced with soluble pentobarbital made after unilateral extirpation of the second and third thoracic segments of the sympathetic trunk, leaving the cervicothoracic ganglion and its connections with the first thoracic nerve and the brachial plexus intact: *A*, upper record, from the side on which operation was done; lower record, from the other side. The stimulus was ice applied to the hind feet. *B*, upper record, from the side on which operation was done; lower record, from the other side. The stimulus was faradic stimulation in the femoral region. Stimulation was begun at the first marker and discontinued at the second.

RESULTS

In both cats and monkeys, application of ice to the soles of the hind feet or mild faradic stimulation of the femoral nerve elicited marked vasoconstriction, as indicated by the volume pulse wave record (figs. 1 and 3 *A*), in the digits of the upper extremity in the intact animal. In animals which had been subjected to extirpation of the second and third thoracic segments of the sympathetic trunk, leaving the first thoracic nerve and the cervicothoracic ganglion with its communicating rami intact, application of ice to the soles of the hind feet sometimes, and faradic stimulation of the femoral nerve always, elicited vasoconstriction in the digits of the upper extremity on the side of the operation

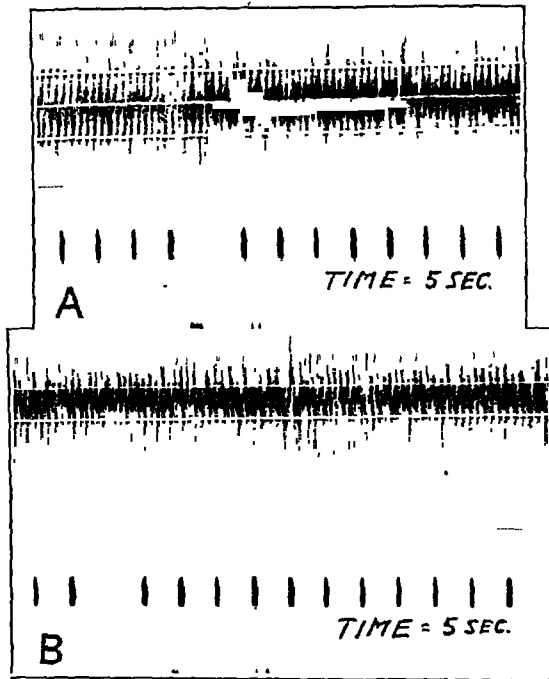


Fig. 2.—Photoelectric plethysmographic records from toe pads of the upper extremity of a cat under anesthesia induced with soluble pentobarbital: *A*, following extirpation of the second and third thoracic segments of the sympathetic trunk; *B*, following extirpation of the cervicothoracic ganglion after removal of the second and third thoracic segments of the sympathetic trunk. Faradic stimulation in the femoral region was begun at the first marker and discontinued at the second.

(figs. 1, 2 *A* and 3 *B*). The change in the amplitude of the volume pulse wave, elicited by the stimulation employed, following extirpation of the second and third thoracic segments of the sympathetic trunk was less marked than that elicited in the intact animals, but always unmistakable. After extirpation of the cervicothoracic ganglion in animals which had previously been subjected to extirpation of the second and third thoracic segments of the sympathetic trunk, the same afferent stimulation usually

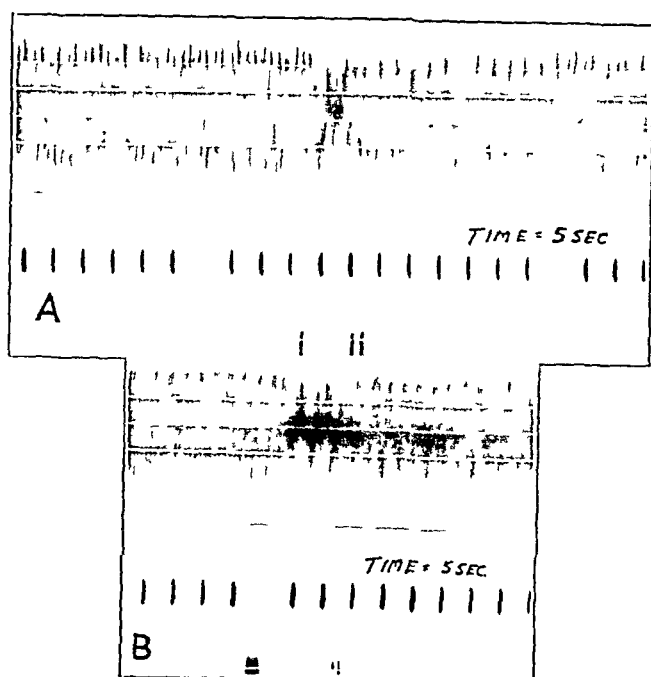


Fig. 3.—Photoelectric plethysmographic records from finger pads of a rhesus monkey under anesthesia induced with soluble pentobarbital: *A*, before operation; *B*, after extirpation of the second and third thoracic segments of the sympathetic trunk. Faradic stimulation in the femoral region was begun at the first marker and discontinued at the second.

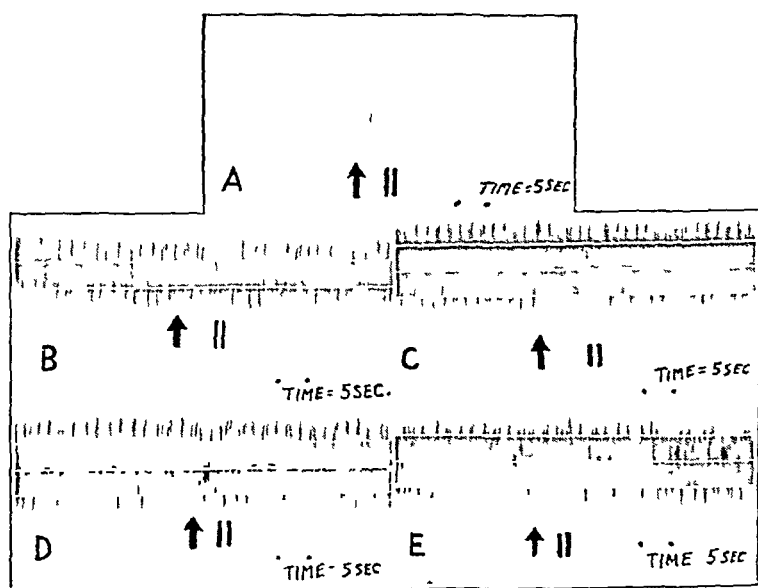


Fig. 4.—Photoelectric plethysmographic records from pads of all the digits of the upper extremity of a rhesus monkey under anesthesia induced with soluble pentobarbital following extirpation of the cervicothoracic ganglion with the second and third thoracic segments of the sympathetic trunk. Faradic stimulation in the femoral region was begun at the arrow and discontinued at the second marker. *A*, thumb; *B*, second digit; *C*, third digit; *D*, fourth digit; *E*, fifth digit

failed to elicit any change in the volume pulse wave in the affected extremity (figs. 2 *B*, and 4 *A*, *B* and *E*). In a few instances, particularly in the monkey, it was possible to elicit a slight degree of reflex vasoconstriction (fig. 4 *C* and *D*), probably due to the presence of sympathetic fibers which join the brachial plexus from the nerves in the vertebral canal, which had not been interrupted.

COMMENT

The data obtained in the present series of experiments prove conclusively that reflex vasoconstriction in the digits of the upper extremity may be elicited after section of all preganglionic fibers below the first thoracic nerve which are involved in the sympathetic innervation of the upper extremity. Preganglionic components of the first thoracic nerve, consequently, must effect synaptic connections with sympathetic ganglion cells the axons of which extend into the upper extremity.

The operative procedure of extirpation of the second and third thoracic segments of the sympathetic trunk, as carried out, insures interruption of all preganglionic components of the second and third thoracic nerves and all preganglionic and postganglionic fibers which ascend in the sympathetic trunk from levels below the third thoracic segment. Care also was taken to interrupt any rami extending from the third thoracic nerve to the second or from the second to the first if such rami were present. The only efferent pathway through which vasoconstrictor impulses could reach the digits of the upper extremity following this operation, with the possible exception of a few sympathetic fibers which ascend in the vertebral canal and join the brachial plexus,⁴ must include preganglionic components of the first thoracic nerve.

It is not without interest that in certain instances after extirpation of the cervicothoracic ganglion in animals in which the second and third thoracic segments of the sympathetic trunk had already been removed, as illustrated in fig. 4, *C* and *D*, afferent stimulation in a lower extremity resulted in slight vasoconstriction in certain of the digits but not in others. This result probably can be explained most satisfactorily on the assumption that the efferent impulses in question were conducted by sympathetic fibers which arise below the third thoracic segment, ascend in the vertebral canal and join the lower cervical and first thoracic nerves. Since but few of these fibers reach the upper extremity, they probably were represented in certain of the digits and not in the others.

The results of the present series of experiments support the assumption that the role of preganglionic components of the first thoracic nerve

4. Van Buskirk, C.: The Nerves in the Vertebral Canal and Their Relation to the Sympathetic Innervation of the Upper Extremities, *Arch. Surg.* **43**:427-432 (Sept.) 1941.

in the sympathetic innervation of the upper extremity is not unimportant and is comparable in the cat and the monkey. If the conditions in man may be regarded as comparable to those in the monkey with respect to the preganglionic components of the first thoracic nerve, it is evident that complete sympathetic denervation of the upper extremity cannot be accomplished by any operative procedure which leaves the cervicothoracic sympathetic ganglion with its gray communicating rami intact and does not interrupt the preganglionic components of the first thoracic nerve.

SUMMARY

In cats and rhesus monkeys, reflex vasoconstriction in the digits of the upper extremity has been demonstrated following extirpation of the second and third thoracic segments of the sympathetic trunk. The first thoracic nerve, consequently, *must include preganglionic components* which are involved in the sympathetic innervation of the upper extremity. The significance of this anatomic fact in relation to sympathetic denervation of the upper extremity is pointed out.

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GUNSHOT WOUNDS OF THE CHEST

A REVIEW OF TWO HUNDRED AND EIGHTY CASES

HARRY G. HARDT JR., M.D.

AND

LINDON SEED, M.D.

CHICAGO

Gunshot wounds of the chest are a common problem of the military surgeon in active warfare, but they are frequently seen also in civil practice in large municipal hospitals. The same principles of therapy apply in both instances, but certain differences are at once apparent. During warfare, more emergency operations are performed; the septic complications are more frequent, and the mortality rate is somewhat greater. In civil practice, gunshot wounds are usually small; there is only a small amount of tissue damage; septic complications are uncommon; recovery is prompt, and the mortality rate is low provided the great vessels are not penetrated (if they are, rapid or immediate death is the rule). These differences are due largely to the penetrating missile. Penetration of the thorax as seen in patients admitted to large municipal hospitals is usually caused by plain or jacketed bullets. In warfare, on the other hand, penetration is often caused by shell fragments, which produce large wounds with extensive tissue damage and often necessitate early operation. With these wounds, septic complications are more numerous, and the mortality rate is somewhat higher. The type of septic complications and the end results are dependent to some extent on the virulence of the prevailing local organisms. Ranson¹ stated that the infections seen by him during the Chinese war appeared to be less virulent than those reported during the first World War.

The records of 280 cases of gunshot wounds of the chest have been reviewed in this series. All of the patients were admitted to Cook County Hospital during the nine year period from 1931 to 1939. To obtain a clear picture of thoracopulmonary wounds only, all cases have

From the Department of Surgery of the University of Illinois College of Medicine and the Cook County Hospital.

1. Ranson, F. T.: Notes on Gunshot Wounds of the Chest, *J. Thoracic Surg.* 9:278-290 (Feb.) 1940.

been deleted in which wounds of the heart or extrathoracic viscera obscured the clinical picture or influenced the course or the treatment of the chest wound.

SUPERFICIAL GUNSHOT WOUNDS OF THE CHEST

There were 130 cases (46.4 per cent) in which there was no evidence that the pleural cavity had been entered by the projectile. Most of these patients had short periods of hospitalization and few serious complications. In 11 cases (7.8 per cent), some infection of the wound developed; this was relieved by incision and drainage or by hot wet dressings. In 1 case, however, an abscess of the chest wall extended into the pleural cavity and caused empyema which required resection of a rib and drainage.

Five patients (3.3 per cent) had simple or comminuted fracture of one rib. Fractured scapula was present in 1 case, and the clavicle was fractured in 1.

In this series there was 1 death due to tetanus. This patient had received 1,500 units of tetanus antitoxin on admission and was treated with large doses of antitoxin and averted with amylene hydrate after the diagnosis was established. She died eighteen days after being shot.

PENETRATING GUNSHOT WOUNDS OF THE CHEST

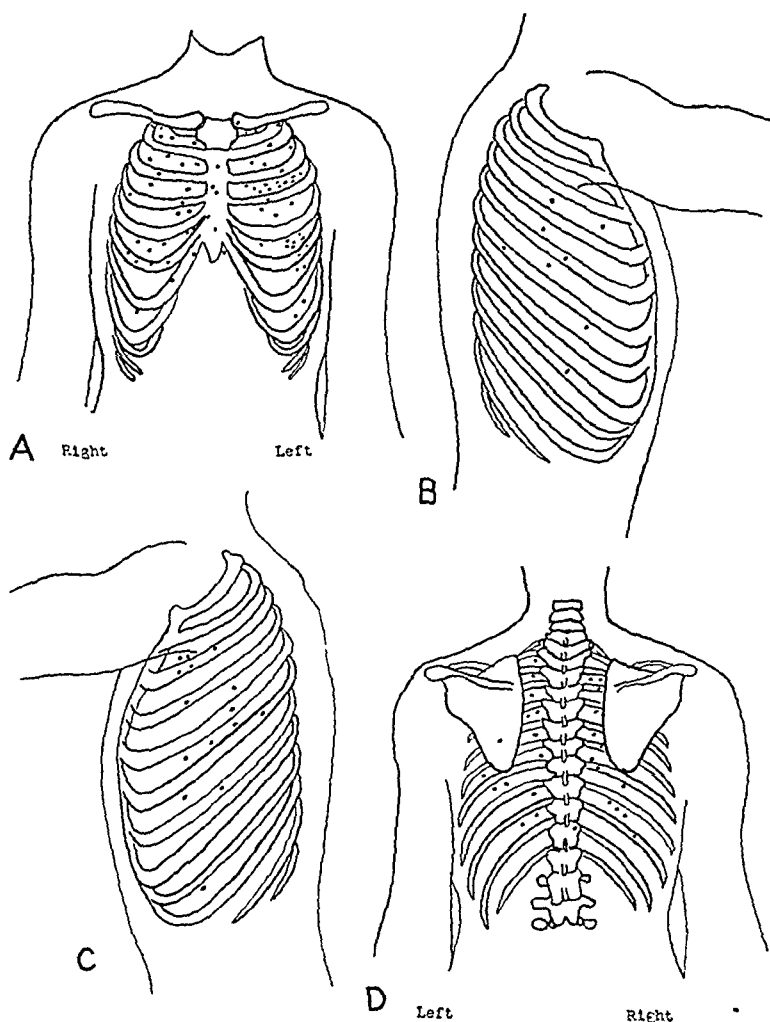
There were 150 patients (53.6 per cent) whose pleural cavity had been penetrated. Of these, 136 were admitted immediately after being shot, while 14 were admitted from forty hours to three weeks later, most of these coming from other hospitals. The wounds were caused by bullets of all the common calibers. There were 2 cases of shotgun wounds; one of these, in which the shot had been fired at close range, was the only case in which open sucking pneumothorax was present. In 78 cases (52 per cent) there was through and through penetration. There were 16 cases (10.6 per cent) in which multiple wounds were present and 5 (3 per cent) in which there was bilateral penetration.

CLINICAL MANIFESTATIONS

Most of the patients admitted were in shock. This was variable but was considered severe in 45 (30 per cent) and moderate in 36 patients (24 per cent). In a few patients no shock was present. Dyspnea in varying degree and pain in the chest were common complaints. Hemoptysis occurred in 73 (48.7 per cent), but in many of these it was small in amount and did not recur.

Subcutaneous Emphysema.—Subcutaneous emphysema is a common finding with penetrating wounds of the chest. It was present in 61 (40.7 per cent) of the cases and was considered marked in 15 (10 per cent). None of these patients received any active therapy for emphysema.

Subcutaneous emphysema usually arises at the site of the wound either from air sucked in through the wound or from air extravasated from the pleural cavity or the lungs. A second form of emphysema, described by Berry,² is said to arise from a tear in the mediastinal pleura. In this form of emphysema air enters the mediastinum and ascends into the neck; from here it may extend in any direction in the



Wounds of entrance: *A*, in the anterior part of the chest; *B*, in the region of the right axilla; *C*, in the region of the left axilla; *D*, in the posterior part of the chest.

subcutaneous tissue. Occasionally, this causes such severe compression of the structures in the mediastinum and the neck that multiple incisions through the fascia above the episternal notch are necessary to release

2. Berry, F. B.: Wounds of the Thoracic Viscera, *Am. J. Surg.* 39:12-17 (Jan.) 1938.

the air. Mediastinal compression is rather infrequent, inasmuch as active treatment was unnecessary in any case in this series and Stenbuck³ reported that surgical intervention was necessary in only 2 cases in six years at Harlem Hospital.

Hemothorax and Hemopneumothorax.—In the series of cases of penetrating wounds, hemothorax or hemopneumothorax was present in 116 cases (77.2 per cent). Pure hemothorax was present in 55 (36.6 per cent). The amount of blood varied; in some cases it was just enough to obliterate the costophrenic angle, while in others it filled the entire pleural cavity. Hemopneumothorax was present in 61 (40.7 per cent) of the cases. In some of these hemothorax predominated, while in others there was only a small amount of blood but practically complete collapse of the lung. Most of the patients were treated conservatively. Therapeutic aspirations were done only for severe dyspnea and chest pain; diagnostic aspirations were done in most cases and repeated whenever the clinical course suggested the possibility of infection. In 56 cases of hemothorax and hemopneumothorax in which there were no other injuries or complications of any kind, the average hospitalization was thirteen and six-tenths days. These patients usually had fever for several days. In most of them the temperature rarely exceeded 101 F.; occasionally, however, temperatures of 103 F. or over were recorded. The average number of days in which the temperature reached 100 F. or over was six and nine tenths. *It is of interest to note that 6 of these patients had extended periods of hospitalization of five weeks or more. These patients had elevations of temperature reaching 100 F. daily for twenty-four to thirty-six days. Repeated aspirations were sterile. Why these patients should have had such a protracted convalescence is a matter of conjecture.*

Small simple hemothorax usually responds well when treated expectantly. This opinion is also held by Elkin,⁴ Chandler and associates,⁵ Harrington⁶ and others. In cases of large simple hemothorax, aspiration and air replacement comprise the method of choice according to Foster and Prey⁷ and Hegner⁸; in fact, these authors have recom-

3. Stenbuck, J. R.: Traumatic Subcutaneous Emphysema of Thoracic Origin, New York State J. Med. **37**:395-399 (Feb. 15) 1937.

4. Elkin, D. C.: Wounds of Thoracic Viscera, J. A. M. A. **107**:181-184 (July 18) 1936.

5. Chandler, F. G.; Mason, G. A.; Livingston, J. L.; Edwards, T., and others: A Discussion on the Treatment of Traumatic Hemothorax, Proc. Roy. Soc. Med. **34**:73-81 (Dec.) 1940.

6. Harrington, S. W.: Wounds of the Chest and Abdomen, Proc. Staff Meet., Mayo Clin. **15**:808-811 (Dec. 18) 1940.

7. Foster, J. M., Jr., and Prey, D.: The Treatment of Acute Traumatic Hemothorax, Ann. Surg. **100**:422-428 (Sept.) 1934.

8. Hegner, C. F.: Surgical Treatment of Injuries of the Chest, Am. J. Surg. **47**:394-407 (Feb.) 1940.

mended this form of treatment even for small hemothorax. Aspiration and air replacement is a simple procedure, practically devoid of danger after the initial forty-eight hours; it shortens the period of convalescence, and it is said by Foster and Prey to prevent the late complications of infection and deforming adhesions. In cases of persistent acute hemorrhage, aspiration and air replacement may be lifesaving; the treatment is universally recommended in the presence of severe dyspnea. In the series here reported, aspiration and air replacement were not used; the convalescence was not unduly prolonged in most cases, and the incidence of complications was small. Sandison and Elkin⁹ have shown that blood and blood clots experimentally placed in the pleural cavity of dogs are rapidly absorbed and that their presence does not predispose to infection. Elkin utilized aspiration alone for pain and severe dyspnea in a group of 553 patients with penetrating wounds of the chest and reported a low incidence of septic complications. Allen¹⁰ has suggested that hemothorax may well be treated by seepage with the wound in a dependent position for drainage. This method has also been successfully employed by Duff.¹¹ Autotransfusion of the blood aspirated from the pleural cavity has been recommended by Brown,¹² Butler¹³ and Hegner.

For patients with extensive laceration of the lung in addition to hemothorax (a condition commonly seen in warfare), active therapy is certainly indicated. Aspiration and air replacement may be successfully utilized in some cases, but according to Chandler and associates, thoracotomy and repair of the lung will be required in many cases. In a small number of cases hemothorax arises from a severed intercostal or internal mammary artery. In these cases aspiration and air replacement are of no value; the bleeding vessel must be ligated, but frequently the pleural cavity need not be entered.

It seems reasonable to treat small to moderate hemothorax expectantly. Aspiration and air replacement should be used for large hemothorax and in the presence of respiratory embarrassment; open operation should be used when there is extensive lung laceration and when hemothorax is complicated by the presence of a large intrapleural foreign body. Bleeding intercostal and internal mammary vessels must

9. Sandison, J. C., and Elkin, D. C.: Penetrating Wounds of the Chest with Studies on Experimental Hemothorax, *J. Thoracic Surg.* **2**:453-467 (June) 1933.

10. Allen, D. S.: The Treatment of Penetrating Wounds of the Pleural Cavity, *Arch. Surg.* **21**:1161-1172 (Dec.) 1930.

11. Duff, P. H.: Penetrating Wounds of the Chest in Civil Life, *Texas State J. Med.* **29**:438-441 (Nov.) 1933.

12. Brown, A. L., and Debenham, M. W.: Autotransfusion: Use of Blood from Hemothorax, *J. A. M. A.* **96**:1223-1225 (April 11) 1931.

13. Butler, E.: Injuries of the Chest and Abdomen, *Surg., Gynec. & Obst.* **66**:448-453 (Feb.) 1938.

be ligated. Of course all treatment is countermanded until the initial shock is effectively combated.

Pneumothorax.—In cases of gunshot wounds in civil life pneumothorax alone is an infrequent finding. It was seen in only 3 (2 per cent) of the cases of penetrating wounds in our series. Open pneumothorax, caused by a sucking wound, must receive immediate attention to prevent mediastinal shift and severe respiratory embarrassment. The wound must be closed immediately, preferably by operative repair if the patient's condition warrants. An air-tight dressing may be employed in emergencies.

Ordinarily, pneumothorax prevents further hemorrhage and promotes healing by collapse of the lung; for this reason no immediate correction is indicated. Occasionally, a valvelike wound of the lung permits the entrance of air into the pleural cavity but prevents its exit. Constantly mounting pleural pressure results, and this positive pressure will interfere markedly with respirations and may demand immediate treatment. Usually aspiration of air is sufficient, but occasionally the aspirating needle must be connected to a tube under water to permit the periodic egress of the enclosed air with respiratory movement. In a few cases even this is insufficient, and operative repair is necessary. This is commonly called tension pneumothorax. There were no cases of this kind in this series.

COMPLICATIONS

Of the complications, infection is by far the most important, excluding of course complicating injury to other organs.

Infection.—There were only 5 cases (3.3 per cent) in which there was infection of the wall of the chest in the series of cases of penetrating wounds. In addition to the single case of empyema following infection of the wall of the chest previously mentioned, there were 8 cases (5.3 per cent) of empyema. Four of the patients were admitted from other hospitals with already developed empyema. Empyema developed in our wards in only 4 (2.6 per cent) of the cases. In 1 of the remaining 4 patients, empyema developed after infection of a wound in the chest wall. In 2 patients with transection of the thoracic part of the spinal cord, empyema developed late in the course of the illness after several sterile aspirations. In the remaining case empyema was discovered at postmortem examination. Four of the 8 patients died. Cultures made in 4 of the cases revealed a different organism in each case; hemolytic streptococcus, staphylococcus, pneumococcus and *Bacillus coli* were present in 1 case each. In 1 patient, gangrene of one lobe of the lung developed; this lobe was removed, and the patient recovered. Empyema

was treated by rib resection and drainage in 3 cases and by closed drainage in 2. Two patients in desperate general condition were treated by repeated aspiration. No cases of lung abscess occurred.

Septic complications in these cases are infrequent in civil life. Elkin reported an incidence of empyema of 1.4 per cent in his series, while Boland¹⁴ reported 1.7 per cent in his series. In wartime, however, empyema is much more common; Heuer and associates¹⁵ found empyema in 17 per cent of their cases, while Bradford¹⁶ reported an incidence of 25 per cent.

Infected hemothorax should first be treated by repeated aspiration. This was recommended by Chandler and associates for the purpose of localizing the infection and allowing time for the mediastinum to become stabilized. They stated that the principle emphasized in the treatment of empyema generally applies to this condition also, namely, that if rib resection is performed early, the resultant mediastinal shift will produce serious respiratory embarrassment and frequently contribute to death. Extensive pneumothorax also is present, and frequently the lung is unable to reexpand because of dense adhesions. Most surgeons agree that rib resection is the treatment of choice after the infection has become localized and the mediastinum fixed. A few surgeons, e. g., Bume and Liu,¹⁷ have recommended aspiration and irrigation as long as the patient continues to improve on this regimen.

Fractures.—There were fractured ribs in 15 patients (10 per cent) with penetrating wounds. More than one rib was fractured in 5 patients (3.3 per cent); 1 had compound fractures. There were 7 patients with fractured vertebrae (4.6 per cent); 2 had fractured scapulas.

Spinal Cord Injuries.—Damage to the spinal cord was the only severe extrapulmonary complication in this series. There were 8 cases in which damage was present. Five of the patients died. Complete transection was observed in 7 cases; 1 patient had a Brown-Séquard type of hemisection. Laminectomy was done in 1 case.

RESULTS

Twenty-six patients with penetrating wounds died—a total mortality rate of 17.3 per cent. Fifteen of these patients, admitted in a state of profound shock, died within twenty-four hours; the mortality rate after

14. Boland, F. K.: Traumatic Surgery of the Lungs and Pleura: Analysis of 1,009 Cases of Penetrating Wounds, *Ann. Surg.* **104**:572-578 (Oct.) 1936.

15. Heuer, G. J.; Pratt, G. P., and Mason, V. R.: Penetrating War Wounds of the Chest, *Ann. Surg.* **72**:352-369 (Sept.) 1920.

16. Bradford, J. R.: Gunshot Wounds of the Chest, *Lancet* **1**:227-232 (Jan. 29) 1916.

17. Bume, G. F., and Liu, W. L.: Gunshot Wounds of the Chest: Medico-Surgical Experiences During the Conflict in Shanghai, *Chinese M. J.* **47**:357-363 (April) 1933.

twenty-four hours was 7.3 per cent. Of the remaining 11 patients, 4 had transection of the thoracic spinal cord. If these are excluded, the mortality rate for thoracopulmonary wounds alone after the first twenty-four hours is 4.6 per cent.

POSTMORTEM OBSERVATIONS

Reports of the coroner's postmortem examination were available in 18 cases. Deaths in the first twenty-four hours were uniformly due to

*Clinical Manifestations and Mortality Rates of Various Series of Cases of Penetrating Wounds of the Chest Reported in the Literature**

Authors	Cases	Clinical Manifestations					Mortality Rates		
		Subcutaneous Emphysema, per Cent	Pneumothorax, per Cent	Hemothorax, per Cent	Hemopneumothorax, per Cent	Hemoptysis, per Cent	Pleural Infection, per Cent	Total, per Cent	After Deducting Deaths Within First 24 Hr., per Cent
Connors, J. F., and Sten- back, J. B. <i>Ann Surg</i> 97: 528-546 (April) 1933		40	12				6	12.6	
Flkin ⁴	553	10	24	37	56		14		0
Steinke, C. R. <i>J Thoracic Surg.</i> 8: 658-665 (Aug) 1939	87	25	18	36.7	11.5	43		28.7	11.6
Boland ¹⁴	1,009	15	19	25	38	..	1.7	13	9
Stephens, H. W., and Cohn, S. <i>California & West Med</i> 35: 331-336 (Nov) 1930	102		29.5	71	24.5		12.5	16.5	6.8
Heuer, Pratt and Mason ¹⁵	160	11 (exten- sive)	14 (pure)	81	11		17	26.6	13
Hardt and Seed	150	40.7 (10, ex- tensive)	2	36.6	40.7	48.7	5.3	17.3	7.3

* Both knife and gunshot wounds are included in all series except those of Heuer, Pratt and Mason and of Hardt and Seed.

hemorrhage. Reports were available for 9 of the patients who died within twenty-four hours. One of these had large bilateral hemothorax, while 3 had large unilateral hemothorax. In 2 patients the parenchyma of the lung was extensively infiltrated with blood, 1 of these patients had small hemothorax in addition, while in the other the pleural cavities were obliterated by old adhesions. One patient had moderate hemothorax and huge bulging mediastinal hematoma. In 1 there was moderate hemothorax but with penetration of all three lobes of the right lung. The extent of the remaining patient's hemothorax was not

recorded. All 6 patients on whom no postmortem examination was performed died in profound shock.

Reports of the postmortem examination were available for 9 of 11 patients who lived longer than twenty-four hours. Two of these lived less than forty-eight hours, and hemothorax was present in both. In addition, 1 had old localized peritonitis (ulcerative enterotyphlitis *Endamoeba histolytica*). Four patients had lesions of the thoracic portion of the spinal cord. In addition, 1 had what is described as pyohemothorax; another, serofibrinous purulent pleuritis. One patient had perforation of both lungs with unilateral hemothorax. One patient had empyema; the lung of the remaining patient was densely infiltrated with blood. Of 2 patients for whom no autopsy was performed, 1 had pneumonia according to the clinical diagnosis. The second patient had empyema which had been drained; however, a brain abscess had developed.

COMMENT

In the series of cases of penetrating wounds of the chest, the diagnosis of fractured ribs was made in only 10 per cent. This is probably a low figure since it is often difficult to be sure of this complication in a patient with superficial wounds and in shock. In many cases roentgen evidence is obscured by hemothorax. It is of interest that rib fracture was present in 50 per cent of the patients who came to postmortem examination.

According to Heuer, Pratt and Mason, the indications for early operation used by the American Medical Corps during the first World War were: (1) open sucking pneumothorax; (2) acute continuous hemorrhage; (3) large intrapleural or extrapleural foreign bodies, and (4) extensive rib fractures. To these the British author Gask¹⁸ added: (5) ragged wounds of the soft parts; (6) persistent bleeding from the parietal wound; (7) compound rib fractures; (8) penetrating rib splinters; (9) tension pneumothorax, and (10) large clotted hemothorax. The German authors Landois¹⁹ and Bumm²⁰ in articles covering the Polish and other campaigns mentioned approximately the same indications. Operations have been advised as soon as the patients recover from the initial shock. Careful review of the cases in our series in the light of these indications reveals few in which there were any

18. Gask, G. E.: Gunshot Wounds of the Chest, *Brit. M. J.* **1**:1043-1045 (May 20) 1939.

19. Landois, F.: The Evaluation and Therapy of Thoracic and Pulmonary Gunshot Wounds at Front, *Med. Klin.* **36**:449-452 (April 26) 1940.

20. Bumm, E.: Fundamentals of Treatment of Gunshot Wounds of the Thorax and Lungs: Experiences During the Polish Campaign, *Med. Welt* **14**:237-239 (March 9) 1940.

indications for early operation. Seventy-three per cent of the men operated on by Heuer and associates had large sucking open pneumothorax. In our series only 1 patient had this condition, and he died five hours after admission in profound shock. He had been given an air-tight dressing and shock treatment. Four of the patients mentioned by Heuer and associates had large intrapleural foreign bodies; 4 were operated on because of acute hemorrhage, and there was a question of injury in the abdominal cavity of 6 patients. Only among those with acute hemorrhage can we find any patients who might have been saved by early operation, and it is difficult in retrospect to be sure that an operation was needed even for them.

The early death of patients with penetrating wounds is almost exclusively due to hemorrhage. Bleeding may be intrapleural (hemothorax), or if the pleural cavity is obliterated or the wound in the lung sealed, blood may fill the parenchyma of the lung. Occasionally, bleeding from the large vessels in the mediastinum may produce large mediastinal hematoma and death. In deaths after forty-eight hours, lesions of the spinal cord and sepsis in the pleural cavity account for a large majority of the deaths.

CONCLUSIONS

Thoracopulmonary gunshot wounds occurring in civil practice, if not rapidly fatal, are characterized by their slight tissue damage, low incidence of septic complications, early recovery and low mortality rate.

Hemorrhage is the common cause of early death. This may take the form of bleeding into the pleural cavity, bleeding into the parenchyma of the lung or bleeding into the mediastinum.

The common causes of late death are lesions of the thoracic portion of the spinal cord and sepsis.

6800 Constance Avenue.

55 East Washington Street

GUNSHOT WOUNDS OF THE BRAIN

REPORT OF TWO UNUSUAL COMPLICATIONS; BIFRONTAL PNEUMO-
CEPHALUS AND LOOSE BULLET IN THE LATERAL VENTRICLE

ELDRIDGE CAMPBELL, M.D.

W. P. HOWARD, M.D.

AND

W. B. WEARY, M.D.

ALBANY, N. Y.

Bullet wounds of the brain are by no means invariably fatal. If not killed outright by injury to vital centers or by massive hemorrhage and edema, many persons so wounded should recover. Their survival is made hazardous by hemorrhage, by necrosis and edema of the brain tissue and by infection. Even under the unfavorable conditions prevailing at the front during the last war, Cushing¹ was able to report a mortality rate of only 28.8 per cent² in a large series of cases.

In a small group of patients treated by us, two somewhat unusual complications were encountered. These were bilateral pneumocephalus and the presence of a loose bullet in the lateral ventricle. With military assignments in prospect for many, the records of these patients are of some interest.

REPORT OF CASES

CASE 1.—The patient had a gunshot wound of the brain with division of the left optic nerve. There were fractures of both frontal sinuses and the left cribriform plate. Bilateral pneumocephalus developed. Fascia lata repair of the dural lacerations were done and recovery followed.

B. M., a 21 year old white man, was referred to Albany Hospital by Dr. L. W. Locke of Utica, N. Y., and Dr. Wardner D. Ayer of Syracuse, N. Y., on July 22, 1940. Twelve days previously, he had been accidentally shot at close range by a .22 caliber rifle. The bullet entered through the wall of the left orbit, where it fragmented. Its course through the apex of the orbit into the floor of the anterior fossa and in part through the the fractured frontal bone could subsequently be

From the Departments of Neurosurgery and Roentgenology, Albany Medical College.

Read at the annual meeting of the Harvey Cushing Society, Rochester, N. Y., May 30, 1941.

1. Cushing, H.: Notes on Penetrating Wounds of the Brain, Brit. M. J. 1:221, 1918; A Study of a Series of Wounds Involving the Brain and Its Enveloping Structures, Brit. J. Surg. 5:20, 1918.

2. This figure does not include those patients who died before reaching the hospital.

traced in roentgenograms (fig. 1) from the position of the metallic particles. One piece could be both seen and felt beneath the skin of the right side of the forehead. The inner walls of the frontal and ethmoid sinuses were seen to be fractured. It was obvious from the direction taken by some bits of lead that both frontal poles of the brain had been injured.

At no time had the patient been unconscious or drowsy. While he had been immediately blinded in the left eye, vision in the right remained good. On one occasion only—the day following the injury—a bloody watery discharge from the nose had been observed. During the first week, he complained of left frontal and occipital headaches and at times of nausea and vomiting. There had been short periods of mental confusion. He had only slight fever and no paralysis or convulsions.

On admission to the hospital, twelve days after injury, the temperature and the pulse and respiration rates were normal. He was at times disoriented and inattentive. The wound of entry was apparently granulating satisfactorily. The left eye was proptosed by a large orbital hematoma and was blind and immobile. The left corneal reflex was absent, and sensation was diminished over the supra-

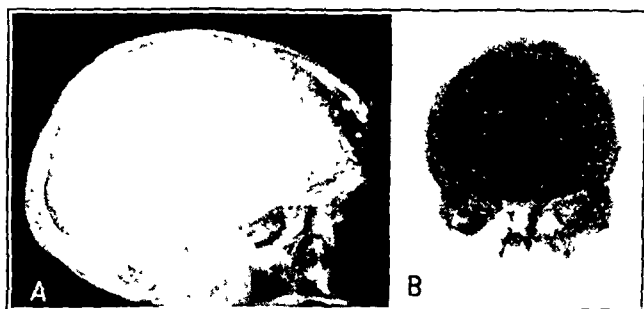


Fig. 1 (case 1).—*A*, lateral roentgenogram of the skull made two weeks after injury. The fragmentation of the lead bullet and the expanding fracture of the right frontal bone are evident. (Fracture lines extending through the frontal and ethmoid sinuses were clearly visible on stereoscopic examination.) *B*, the antero-posterior relation of the bullet tract to the frontal and ethmoid sinuses is shown. No intracranial air was present.

orbital and infraorbital areas on the left. Anosmia was present bilaterally. There was marked photophobia. The neck was rather stiff. Sustained ankle clonus could be elicited on each side. The remainder of the neurologic findings were normal.

Laboratory Data.—The blood count showed 10,600 white cells. Lumbar puncture revealed a pressure of 180 mm. of water. The cerebrospinal fluid was slightly xanthochromic and contained 19 polymorphonuclear leukocytes and 1 red blood cell per cubic millimeter. The total protein of the spinal fluid was 34 mg. per hundred cubic centimeters. The spinal fluid Wassermann test was negative.

Gradual improvement was observed until the twelfth day after admission, when a sore throat developed, and the temperature rose to 102 F. Although the stiffness of the neck had disappeared, the Kernig signs remained mildly positive. Elevation of temperature continued for the next week. During this time the leukocyte count in the blood was found to be normal, and the cell count in the spinal fluid was

never in excess of 6 white blood cells per cubic millimeter. On one occasion the pressure of the spinal fluid was 45 mm. of water, and on another it was practically atmospheric, although when the patient coughed it would rise to 100 mm.

During the next two weeks the patient again improved slowly, although at times he was confused and somewhat disoriented or, again, childish and emotionally unstable. During this time he began to complain of headaches in both the temporal and the occipital region. Not infrequently he became faint and vomited on sitting up. The spinal fluid pressure remained low (35 mm. of water), and the cell count revealed 10 lymphocytes per cubic millimeter.

Except on the day following the injury, rhinorrhea was not observed by the patient nor by any of his attendants until the following week—about a month and a half after the injury. He obeyed instructions not to blow his nose and so far as is known had not sneezed. Roentgenograms taken at that time showed bifrontal pneumocephalus (fig. 2). In retrospect, it seems likely that rhinorrhea had existed intermittently for some time and was responsible for the faintness, the nausea and

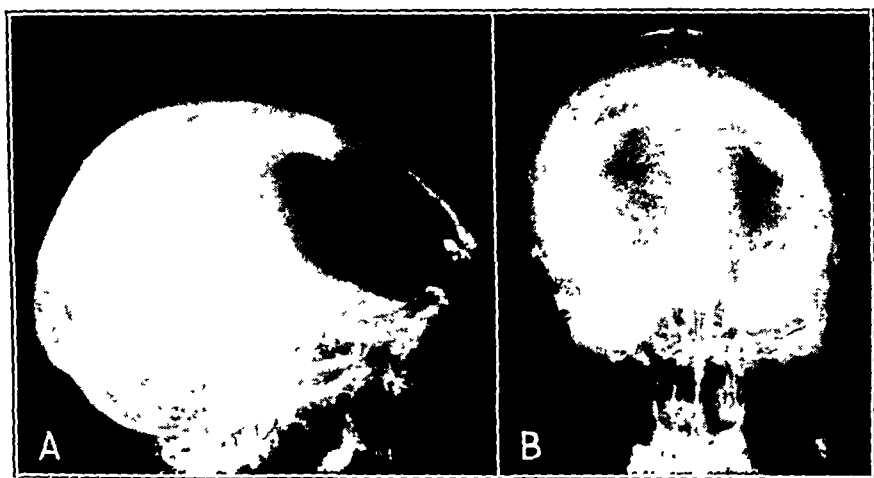


Fig. 2 (case 1).—*A*, lateral roentgenogram of the skull taken six weeks after the injury showing huge frontal pneumocephalus. *B*, posteroanterior roentgenogram showing bifrontal pneumocephalus. Note the fistulous openings in the frontal and ethmoid regions.

the headache which occurred on sitting up, and that it accounted also for the low spinal fluid pressures.

From a careful stereoscopic examination of the roentgenograms, fractures in the inner walls of the frontal and ethmoid sinuses on either side appeared capable of harboring fistulas. In any case, it was deemed necessary to explore both frontal fossae simultaneously.

Operation.—Operation was performed on Jan. 3, 1941. With the patient under anesthesia induced with ether and avertin with amylene hydrate, a coronal scalp incision was made, exposing both frontal bones. A small bone flap was then turned down on each side and hinged to the temporal muscle. There was no increase of intracranial pressure. The dura on the right side was adherent to the adjacent comminuted fracture, where the largest of the missiles had emerged. When the dura was opened, large, smooth, clean-looking cavities were found in

each frontal pole. These communicated through a bullet hole in the falx. Neither ventricle had been entered. Further inspection revealed fistulous openings through the shattered inner plates of both frontal sinuses and the left cribriform plate.

The dura was stripped from the base until the perforations were entirely in view externally, and then a large piece of fascia lata was snugly sutured in place on each side. Care was taken that the fascial patches overlapped the dura by at least 0.5 cm. everywhere, in the belief that this would facilitate the sealing-off process. The bone flaps were replaced, and the muscle, the galea and the skin were closed in layers with interrupted sutures of fine silk without drainage.

Convalescence was uneventful. The wounds healed by first intention. The patient's mind appeared to be clear, and he no longer acted in a childish manner. Save for blindness in the left eye and persistent anosmia, the neurologic abnormalities



Fig. 3 (case 1).—Photograph of the patient taken eight months after operation.

had entirely disappeared at the time of his discharge on January 29. Within two months he returned to work as a bank teller (fig. 3). At the time of writing, he has had no complaints for the past nine months.

Pneumocephalus³ is a well known complication of cerebrospinal fluid fistulas which traverse the frontal, ethmoid, sphenoid or mastoid sinuses.⁴ In civil life, fracture, tumor and infection are the more usual causes, although fistulas of "spontaneous" origin have been recorded. During

3. Dandy, W. E.: (a) Pneumocephalus, *Arch. Surg.* **12**:949 (May) 1926. (b) Pneumocephalus, in Lewis, D.: *Practice of Surgery*, Hagerstown, Md., W. F. Prior Company, Inc., 1932, vol. 12, chap. 1, p. 311.

4. Woodhall, B., and Baker, T. W.: Pneumatocoele Occipitalis, *Arch. Surg.* **42**:858 (May) 1941.

the last war, a number of cases were reported in which gunshot wounds were responsible. Any act which raises the intranasal air pressure, such as sneezing or blowing the nose, can force air through the fistula into the cranial cavity, where it may be trapped by the valvelike action of the adjacent meninges or the brain. The air may be located in the subdural or subarachnoid spaces, within the substance of the cerebrum or in the ventricles. Our patient was rather unusual in that he had two large air pockets, one in each frontal lobe, which communicated through an opening in the falx, and in that fistulous openings were present in both frontal sinuses and through the left cribriform plate. A fatal case of bilateral frontal pneumocephalus was reported by Lewis.^{4a}

The symptoms of pneumocephalus are those of increased intracranial pressure and of the local destructive effects of an intermittently expanding air globule. While healing may take place spontaneously,⁵ death occurs from intracranial pressure or infection in about half the cases in which treatment is not given.

Pneumocephalus is curable only by secure closure of the fistula; this has been pointed out by Dandy,³ Cushing⁶ and others.⁷ Closure of the fistula can best be accomplished by suture or fascial repair of the dural laceration. If pneumocephalus is situated at the frontal⁸ or mastoid^{3a} sinuses, closure may be effected through a relatively small exposure, although in the majority of instances a low-placed osteoplastic bone flap is required. The approximate location of the opening can usually be determined by roentgen demonstration of a fracture through the sinus and of the corresponding location of the air. The latter is released at operation through a ventricular needle.

4a. Lewis, A. J.: Traumatic Pneumocephalus, *Brain* **51**:221 (June) 1928.

5. Horrax, G.: Intracranial Aerocoele Following Fracture of Skull, *Ann. Surg.* **73**:18 (Jan.) 1921.

6. Cushing, H.: Experiences with Orbito-Ethmoidal Osteomata Having Intracranial Complications, with a Report of Four Cases, *Surg., Gynec. & Obst.* **44**: 721 (June) 1927; *J. Am. S. A.* **45**:1, 1927.

7. (a) Teachenor, F. R.: Intracranial Complications of Fistulae of Skull Involving Frontal Sinus, *J. A. M. A.* **88**:987 (March 26) 1927. (b) Munro, D.: The Modern Treatment of Craniocerebral Injuries, with Especial Reference to the Maximum Permissible Mortality and Morbidity, *New England J. Med.* **213**:893 (Nov. 7) 1935. (c) Cairns, H.: Injuries of the Frontal and Ethmoidal Sinuses with Special Reference to Cerebrospinal Rhinorrhea and Aerocoeles, *J. Laryng. & Otol.* **52**:589 (Sept.) 1937. (d) Coleman, C. C.: Fracture of the Skull Involving the Paranasal Sinuses and Mastoids, *J. A. M. A.* **109**:1613 (Nov. 13) 1937. (e) Campbell, E. H., and Gottschalk, R. B.: Osteoma of Frontal Sinus and Penetration of Lateral Ventricle, with Intermittent Pneumocephalus, *ibid.* **111**:239 (July 16) 1938.

8. Dandy.^{3a} Teachenor.^{7a}

If the opening lies in the cribriform plate, it may sometimes be seen through a nasal speculum, as in the case hereinafter cited. While healing has occasionally followed repeated local applications of a caustic,⁹ such procedures have been condemned¹⁰ since the results are uncertain and the patient may die from pressure or infection during the prolonged period usually required for treatment.

In the treatment of gunshot wounds of the brain, Cushing,¹ Horrax,¹¹ Van Wagenen¹² and others have shown that it is advisable to débride the entire wound—scalp, skull and brain—soon after the injury is received. When at all practicable, dural lacerations in the region of the air sinuses should be sought for and carefully closed at that time. It is probable that both local and general treatment with sulfanilamide or one of its derivatives will prove advantageous. Cerebrospinal fistulas through the frontal sinuses are readily accessible and may be repaired by simple suture of the dura or by fascial transplant.

Such a procedure was delayed in case 1, since the patient was apparently doing well when first seen two weeks after the injury, since the wound of entry was filled with none too clean-looking granulation tissue and since we found no evidence of pneumocephalus. In this particular instance, it is possible that had an operation been attempted immediately following the accident, the patient might not have tolerated bifrontal débridement and repair of dural defects in both anterior fossae. Earlier surgical intervention, however, would probably have prevented some of the loss of cerebral tissue caused by the enlarging pneumatoceles and would have shortened the stay in the hospital.

Dural lacerations over the cribriform plates are only slightly more difficult to handle. German¹³ ingeniously used a flap of dura cut from the adjacent side of the crista galli. Adson¹⁴ employed a bifrontal flap which permitted the simultaneous exposure of both sides of the cribriform plate. In addition to using the fascia lata in the case already reported,

9. Fox, N.: Cure in a Case of Cerebrospinal Rhinorrhea, *Arch. Otolaryng.* **17**: 85 (Jan.) 1933.

10. Dandy.^{3a} Coleman.^{7d}

11. Horrax, G.: Observations on a Series of Gunshot Wounds of the Head, *Brit. J. Surg.* **7**:10, 1919; A Proposal for the More Radical Treatment of Gunshot Wounds of the Brain, *Canad. M. A. J.* **43**:320, 1940.

12. Van Wagenen, W. P.: Comment on Winslow, P.: Penetrating Wounds and Foreign Bodies of the Brain, *Neurosurg. Ward Rounds* **2** (nos. 3-4):1, 1941.

13. German, W. J.: Cerebrospinal Rhinorrhea—Operative Repair, *Proc. Harvey Cushing Soc.*, 1941, vol. 10.

14. Adson, A. W.: Cerebrospinal Rhinorrhea: Surgical Repair of Craniosinus Fistula, *Ann. Surg.* **114**:697 (Oct.) 1941.

we have employed it in 1 other case. This second cribriform plate fistula occurred in a patient on whom a colleague performed submucous resection of the nasal septum. A gush of spinal fluid was observed when the septum was broken. By means of a nasal speculum, a large dural rent was readily visible through the left cribriform plate. Within an hour, the patient was anesthetized; a low frontal flap was turned down, and the dura was stripped from the floor of the anterior fossa until the tear was in plain view. Repair was then effected by means of a fascial transplant. Recovery was uneventful.

CASE 2.—Gunshot wound of brain was complicated by a free bullet in the left lateral ventricle. The bullet was removed, and recovery ensued.

E. W., a white woman 29 years of age, was referred to Albany Hospital on Aug. 29, 1940, by Dr. B. G. McKillip of Gloversville, N. Y. Three weeks previously, she had been accidentally struck in the left frontal region by a large lead buckshot, approximately through the coronal suture and 2 inches (5 cm.) from the sagittal suture. She was momentarily unconscious and for the next three days was nauseated and vomited. Fever was slight and of short duration. The neck was not stiff. No convulsions had occurred. Headache, which was maximal in the left temple, lasted for two weeks and then subsided. As she was right handed, there was some aphasia at first, which at the time of admission was gradually disappearing. A few days before admission, she suffered a brief attack of headache, nausea and vomiting. Tetanus antitoxin had been administered on the day of the injury.

On examination, she was seen to be alert, cooperative and in no distress. The wound was granulating, and a small bony defect was palpable beneath it. Speech had become normal, and no personality changes or memory defects were observed. There was mild weakness of the right side of the face and the right hand of the upper motor neuron type. The remainder of the neurologic findings were normal.

Laboratory Data.—Roentgenograms of the skull taken during the first week after the accident (fig. 4) disclosed the bullet lying deep within the left frontal lobe near the midline. A fragment of the missile lay just beneath the scalp near the point of entry. Roentgenograms taken two weeks later (fig. 5) showed, to our surprise, that the bullet was then located deep in the left occipital lobe. Since it appeared likely that it lay within the lateral ventricle, fluoroscopy was carried out. When the head was tilted, the bullet was observed to roll freely between the occipital and frontal regions and even part way down into the temporal horn. The patient experienced no abnormal sensation during these maneuvers.

Since she was afebrile and comfortable, it was decided that she should rest at home until the scalp wound was healed before removal of the bullet would be undertaken. Within a fortnight, however, she suffered a rather sudden severe headache, principally located in the left frontotemporal region and accompanied by projectile vomiting, photophobia, tinnitus and stiffness of the neck.

On readmission on September 12, the neurologic picture was unaltered, but for the first two days there was an evening rise of temperature to 100 F. (rectal). Slight cervical rigidity was present. The wound healed. There was no leukocytosis. Lumbar puncture revealed clear spinal fluid with an initial pressure of 48 mm. of water and a cell count of 210, approximately 65 per cent of which were poly-

morphonuclear leukocytes, the remainder being lymphocytes. The Pandy test was negative. On September 17, after she had been afebrile for three days, the spinal fluid pressure was found to be 110 mm. of water; the fluid was clear; the total protein content was 95 mg. per hundred cubic centimeters, and the cell count was 363, of which 78 per cent were polymorphonuclear leukocytes.

Reexamination by fluoroscopy at this time revealed the bullet lying in the occipital region and fixed. The visual fields were normal.

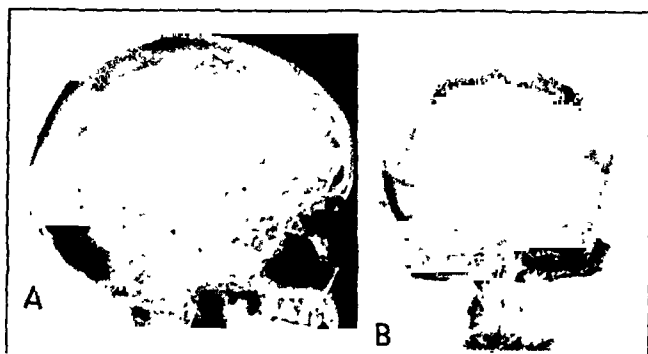


Fig. 4 (case 2).—Lateral (*A*) and posteroanterior (*B*) roentgenograms of the skull taken two weeks after injury. The bullet was located deep within the left frontal lobe, probably in the ventricle. A small fragment of lead remained beneath the scalp near the wound.

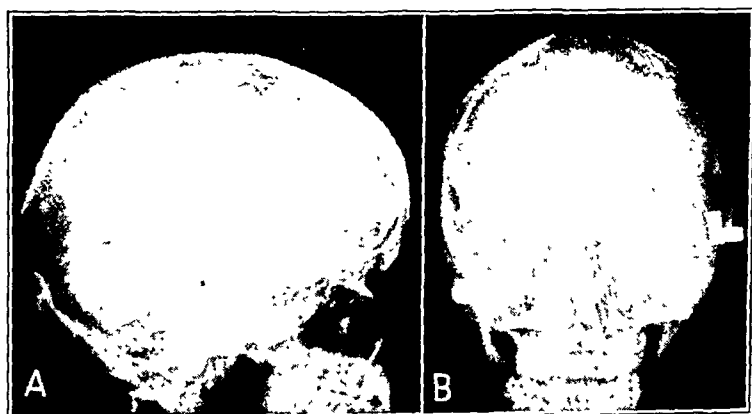


Fig. 5 (case 2).—Lateral (*A*) and anteroposterior (*B*) roentgenograms of the skull showing the bullet in the occipital horn of the left lateral ventricle. Under the fluoroscope the bullet could be observed to roll freely through the lateral ventricle.

Operation.—Operation was done on September 14. After the administration of 1,500 units of tetanus antitoxin on the previous day, a small osteoplastic bone flap was turned down in the left occipital region with the patient under anesthesia induced with ether and avertin with amylene hydrate. The dura and the cerebral cortex appeared normal in every respect. A short longitudinal incision was made into the posterosuperior portion of the lateral ventricle. A nasal speculum was

inserted. The bullet was not in sight. The body and the temporal horn of the ventricle appeared normal. The occipital horn was then inspected, and the bullet was found wedged within. It was removed without bleeding. The wound was closed in the usual manner with fine silk. On culture, the bullet (fig. 6) was sterile.

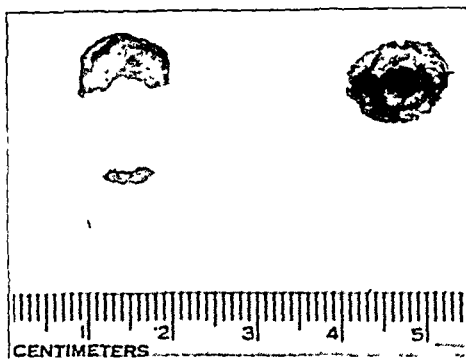


Fig. 6 (case 2).—Photograph of bullet fragments after their removal. The larger was removed from the ventricle.



Fig. 7 (case 2).—Photograph of the patient taken three months after operation.

Convalescence was uneventful. The visual fields remained normal. By the time of discharge, two weeks later, the weakness of the right side of the face and the right hand largely disappeared, as had also all evidence of aphasia. At a recent examination (fig. 7), some eleven months after operation, she was found to have no complaints; the neurologic examination gave entirely normal results, and she was doing her usual housework.

It has long been known that a bullet embedded in the brain may be or become sterile and thereafter be securely enclosed in scar tissue. Some may thus be harbored for years without producing any ill effects, while others may be held responsible for epileptic attacks, headache and vertigo, and their removal, along with as much of the associated cicatrix as possible, is thus indicated.

Foreign bodies in the lateral ventricles have been reported only occasionally. Probably most of them eventually become attached to the ependymal lining or to the choroid plexus.¹⁵ While free, they may, or may not, produce symptoms by irritation or pressure. Our patient had bouts of headache, usually homolateral frontotemporoparietal, accompanied by mild fever, photophobia, tinnitus, slight cervical rigidity and pleocytosis of the spinal fluid. However, cultures of the spinal fluid and of the bullet on removal proved sterile. One of Dandy's patients was described as having such severe symptoms as to necessitate the bullet's removal. Kellhammer's¹⁶ patient experienced no discomfort from a small round shot which wandered freely from the lateral ventricle to the lower part of the spinal canal. No notes are available on the case mentioned by Flesch-Thebesius,¹⁷ and in Van Wagenen's patient, the symptoms were no doubt principally attributable to severe concomitant cerebral damage. From the small number of reported cases available, it appears likely that the majority of such foreign bodies in the lateral ventricles require removal.

SUMMARY

An instance of bilateral frontal pneumocephalus and one of a loose bullet in the lateral ventricle, each following a gunshot wound of the brain, are reported. The methods by which these complications were satisfactorily dealt with are described.

15. Dandy, W. E.: *Cranial Injuries and Their Effect*, in Lewis, D.: *Practice of Surgery*, Hagerstown, Md., W. F. Prior Company, Inc., 1932, vol. 12, chap. 1, pp. 294-295.

16. Kellhammer, G.: *Geschosswanderung in Ventrikelsystem*, *Zentralbl. f. Chir* 66:1773, 1939.

17. Flesch-Thebesius: *Zentralbl. f. Chir.*, 1922, vol. 49, no. 24.

THE HEPATIC (HEPATORENAL) FACTOR IN BURNS

FREDERICK FITZHERBERT BOYCE, M.D.

NEW ORLEANS

The whole truth about any series of burns is seldom if ever known, if for no other reason than that in the great majority of fatal cases the bodies, by law, must be turned over to the coroner, and detailed post-mortem observations are therefore lacking. Related to this lack of pathologic knowledge is McClure's¹ charge that the average physician sees too few burns to know much about them; his estimate was that in ordinary practice he would see 1 burn in every four and one-half years and 1 fatal burn every twenty-three years. Elkinton,² finally, has commented on the surprisingly few studies in the literature on the constitutional aspects of burns, to which any one who has investigated hospital records might well reply that studies of these could scarcely appear in the literature since they are apparently not made on the patient.

A mere statement of mortality, furthermore, by no means tells the whole story of any series of burns. The mortality for the 1,243 burns treated at Charity Hospital of Louisiana at New Orleans in the six and one-half year period ending June 30, 1941 was 17.46 per cent (217 deaths). This is practically identical with the mortality of 17.6 per cent recently reported by McClure and Lam³ from Henry Ford Hospital, Detroit. Both series included a large number of badly burned patients, but the facile statement that series in which high mortality is reported are likely to contain an undue proportion of badly burned patients, and vice versa, is not necessarily true.

Read before the Piedmont Post-Graduate Clinical Assembly, Anderson, S. C., Sept. 9, 1941.

1. McClure, R. D.: The Treatment of the Patient with Severe Burns, *J. A. M. A.* **113**:1808-1812 (Nov. 11) 1939.

2. Elkinton, J. R.: The Systemic Disturbances in Severe Burns, and Their Treatment, *Bull. Ayer Clin. Lab., Pennsylvania Hosp.* **3**:278-291 (Dec.) 1939. Elkinton, J. R.; Wolff, W. A., and Lee, W. E.: Plasma Transfusion in the Treatment of the Fluid Shift in Severe Burns, *Ann. Surg.* **112**:150-157 (July) 1940.

3. McClure, R. D., and Lam, C. R.: Problems in the Treatment of Burns: Liver Necrosis as a Lethal Factor, *South. Surgeon* **9**:223-234 (April) 1940.

One of the paradoxes of burns is that it by no means follows that because a patient's burn is small he will inevitably recover. At Charity Hospital it was possible, by using Berkow's⁴ table, to estimate the extent of body surface involved in 215 of the 217 fatal cases (fig. 1). Since a burn of 50 per cent of body surface ordinarily represents the upper limit of safety, death could reasonably have been anticipated in the 78 fatal cases in which this limit was exceeded. With equal reason, recovery might have been expected in a fair proportion, at least, of the 137 cases in which less than this area was involved. Certainly there was no reason to anticipate a fatal outcome in the 14 cases in which only 15

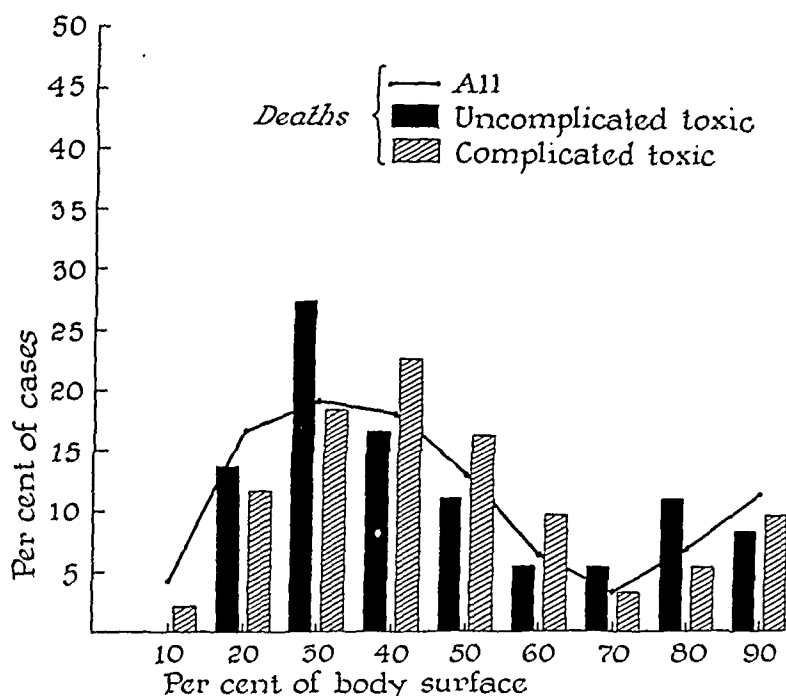


Fig. 1.—Distribution according to body surface involved of 215 fatal burns, 36 of which were associated with uncomplicated, and 92 with complicated, toxicity.

per cent and in the 9 cases in which only 10 per cent of the body surface was involved, or in many of the cases in which the burns were first and second degree (fig. 2). Such facts suggest that considerations other than the merely physical factors of extent and depth must enter into the matter.

An obvious factor is the patient's age, persons at the extremes of life being peculiarly susceptible to death from burns. More than a quarter of the 211 deaths at Charity Hospital in which the age of the

4. Berkow, S. G.: Value of Surface-Area Proportions in the Prognosis of Cutaneous Burns and Scalds, *Am. J. Surg.* 11:315-317 (Feb.) 1931.

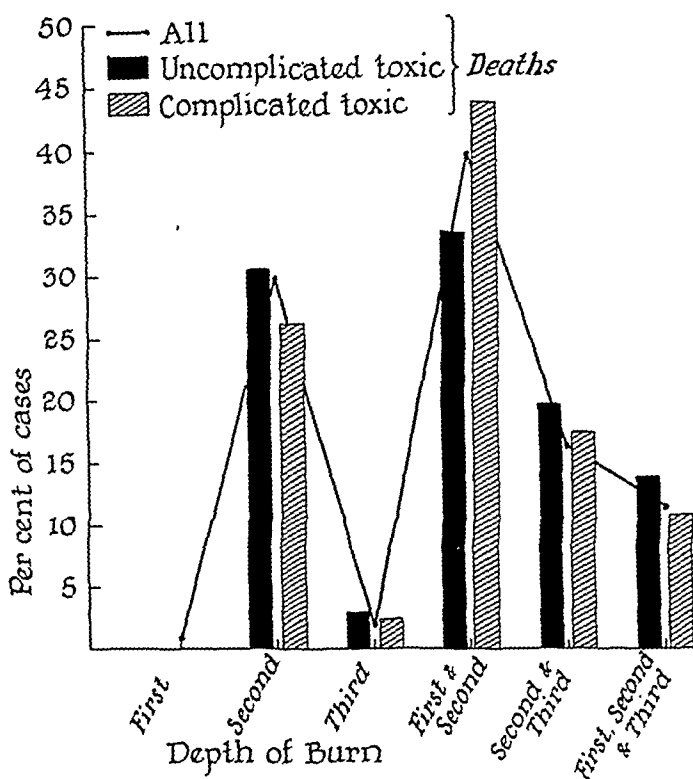


Fig. 2.—Distribution according to degree of 217 fatal burns, 36 of which were associated with uncomplicated, and 92 with complicated, toxicity.

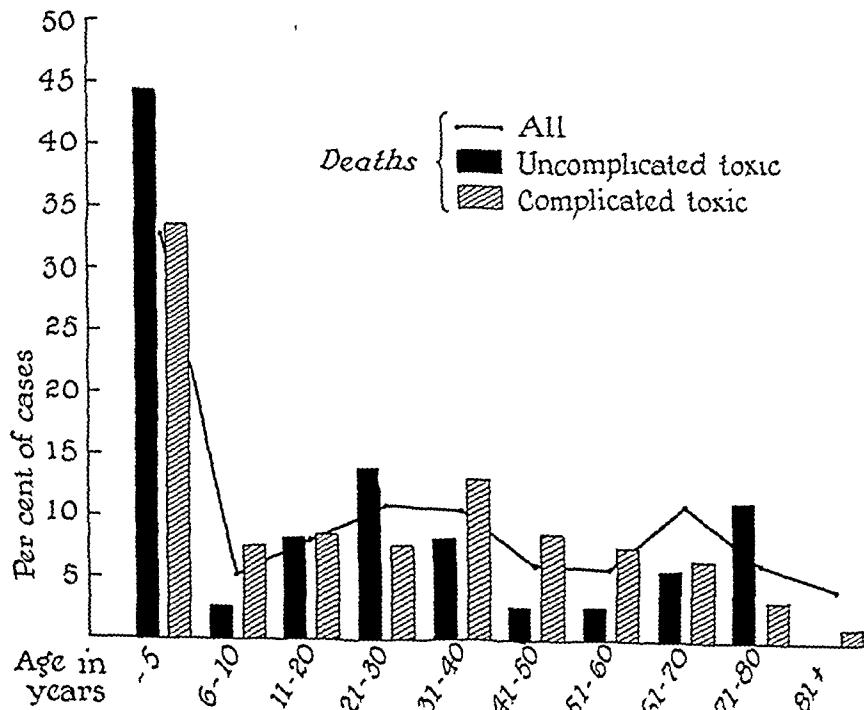


Fig. 3.—Distribution according to age of 211 fatal burns, 36 of which were associated with uncomplicated, and 90 with complicated, toxicity.

patient was known (fig. 3) occurred in children under 5 years of age, and approximately 20 per cent more occurred in patients over 70 years of age.

If there is any ground for complacency in the current belief that the mortality rate associated with burns has improved with the passage of years, the report of Dunbar⁵ from the Glasgow Royal Infirmary, an institution which for fifty years has had special wards for burned patients, is well calculated to destroy it. In an analysis of 10,974 burns treated in the hundred year period ending in 1933, he pointed out that the mortality rate has never been as good in any year since 1868 as it was in many years prior to that date. The comment is the more devastating when one recalls that before that time, because of the incidence of sepsis, gangrene and tetanus in institutions, only the most severely burned patients were hospitalized.

Whatever improvement has occurred in the management of burns is undoubtedly to be traced to the concept of the burned patient as a person whose constitutional state is more serious, actually and potentially, than his local state. It is that concept which makes of special value the studies on burns carried out at Yale University,⁶ at Henry Ford Hospital,⁷ at the University of Pennsylvania⁸ and at the University of Edinburgh.⁹

There is general agreement that all burns of any consequence exhibit certain distinct phases. There is equally general agreement concerning the first of these stages, shock, and the last two stages, the stage of

5. Dunbar, J.: Review of the Burn Cases Treated in the Glasgow Royal Infirmary During the Past Hundred Years (1833-1933), with Some Observations on the Present-Day Treatment, *Glasgow M. J.* **134**:239-255 (Dec.) 1934.

6. Underhill, F. P.; Carrington, G. L.; Kapsinow, R., and Pack, G. T.: Blood Concentration Changes in Extensive Superficial Burns and Their Significance for Systemic Treatment, *Arch. Int. Med.* **32**:31-49 (July) 1923. Underhill, F. P.: Changes in Blood Concentration with Special Reference to the Treatment of Extensive Superficial Burns, *Ann. Surg.* **86**:840-849 (Dec.) 1927. Underhill, F. P., and Kapsinow, R.: The Alleged Toxin of Burned Skin, *J. Lab. & Clin. Med.* **16**:823-830 (May) 1931.

7. (a) Harkins, H. N.: Recent Advances in the Study of Burns, *Surgery* **3**:430-465 (March) 1938. (b) McClure.¹ (c) McClure and Lam.³

8. (a) Wolff, W. A.; Elkinton, J. R., and Rhoads, J. E.: Liver Damage and Dextrose Tolerance in Severe Burns, *Ann. Surg.* **112**:158-160 (July) 1940. (b) Footnote 2.

9. Wilson, W. C.: Extensive Burns and Scalds, *Tr. Med.-Chir. Soc. Edinburgh* **114**:177-192, 1934-1935; in *Edinburgh M. J.*, October 1935. Wilson, W. C.; Jeffrey, J. S.; Roxburgh, A. N., and Stewart, C. P.: Toxin Formation in Burned Tissues, *Brit. J. Surg.* **22**:600-611 (Jan.) 1937. Wilson, W. C.; MacGregor, A. R., and Stewart, C. P.: The Clinical Course and Pathology of Burns and Scalds Under Modern Methods of Treatment, *ibid.* **25**:826-865 (April) 1938. Wilson, W. C.: Cause of Lethal Factors in Burns, *Edinburgh M. J.* **48**:85-93 (Feb.) 1941.

sepsis or infection and the stage of healing. Concerning the stage which follows shock, however, there is no agreement at all.

What this period is called depends chiefly on the point of view of the writer who is describing it. To use the term secondary shock for a stage ordinarily stated to last for several days seems something of a misnomer. To call it the stage of infection is equally incorrect. Aldrich's¹⁰ theory that all findings during it can be explained by bacterial (streptococcic) infection has not been widely approved, and although he was able to culture the organism from the skin in all cases of severe burns and from the blood in all cases in which death occurred, his work has not been confirmed.

So much proof exists for both of the most important theories concerning this stage, the theory of hemoconcentration and the theory of toxemia, that it seems unwise to try to explain it as due exclusively to one pathologic process or to the other. That point of view seems justified even though the theory of hemoconcentration has been definitely established whereas much concerning the toxemic theory, including the isolation and identification of the hypothetic toxin, still remains to be proved.

Hemoconcentration as a possible factor in burns had been suggested as early as 1855, but it remained for Underhill, Kapsinow and their associates⁶ to furnish the conclusive proof. There is now no dispute at all concerning (1) the dangerous diminution of blood volume in burns, due to loss of plasma from the blood and so-called white bleeding at the site of injury, and (2) the resulting hemoconcentration and increase in hematocrit values.

THE TOXEMIC THEORY OF BURNS

Although the toxemic theory of burns has been discussed since 1876, no unanimity exists concerning it, and many observers probably still share Underhill and Kapsinow's point of view, that persistence in the acceptance of a burn toxin is an obstruction to the clarification of the problem.

It must be granted that much of the evidence is conflicting and contradictory. Avdakoff's statement¹¹ in 1876, to the effect that the blood of a burned animal is toxic to a healthy animal, was repeated, with and without proof, until 1923. In that year Robertson and Boyd,¹² in an extensive series of experiments, demonstrated that extracts of burned skin and the blood of burned animals produced toxic symptoms in intact

10. Aldrich, R. H.: *The Role of Infection in Burns*, New England J. Med. 208:299-309 (Feb. 9) 1933.

11. Avdakoff, cited by Wilson and others.⁹

12. Robertson, B., and Boyd, G. L.: *The Toxemia of Severe Superficial Burns*, J. Lab. & Clin. Med. 9:1-14 (Oct.) 1923.

animals and were sometimes lethal. Underhill and Kapsinow⁶ could not confirm these results and expressed the opinion that any lethal factor which might be present was contained in the alcoholic content of the skin extracts.

Similar contradictory results followed Harrison and Blalock's¹³ repetition of Vogt's¹⁴ demonstration that the removal of burned skin prevented the development of toxemia in the injured animal and that its transplantation produced toxemic symptoms in the intact host. In their experiments the animals which were débrided actually died more rapidly than the untreated animals. Two years later Blalock¹⁵ had apparently altered his views, for he made the statement that absorption of the extracts of burned tissue can cause shock and that deaths which occur from three to ten days after severe burns are in large part due to the absorption of products of protein degeneration.

Underhill and his associates⁶ found no evidence of absorption from the burned area after the injection into it of such potent substances as strychnine or of such readily demonstrable substances as methylene blue. Mason and his associates,¹⁶ however, after similar injections of potassium iodide, which is a readily diffusible substance of low molecular weight, found the rate of excretion in the urine to be almost identical in both burned and control animals.

The Japanese investigators are generally in favor of the toxic theory, but their experimental evidence, as Harkins^{7a} has noted, is frequently open to criticism. In the same comprehensive and fair review of the subject, Harkins commented on the seventeen possible toxins listed by Fender¹⁷ and proposed by thirty-four different investigators, but added that the mere multiplicity and confusion of ideas is no argument at all against the validity of the toxemic theory.

Rosenthal¹⁸ found in the blood of human subjects and of certain burned animals a presumably toxic substance which caused contractions

13. Harrison, W. G., and Blalock, A.: A Study of the Cause of Death Following Burns, *Ann. Surg.* **96**:36-39 (July) 1932.

14. Vogt, E.: Versuche über die Uebertragbarkeit des Verbrennungsgiftes, *Ztschr. f. exper. Path. u. Therap.* **11**:191-222 (Oct.) 1912.

15. Blalock, A., in discussion on Heuer, G. J., and Andrus, W. DeW.: The Effect of Adrenal Cortical Extract in Controlling Shock Following the Injection of Aqueous Extracts of Closed Intestinal Loops, *Ann. Surg.* **100**:734-749 (Oct.) 1934.

16. Mason, E. C.; Paxton, P., and Shoemaker, H. A.: A Comparison of the Rate of Absorption from Normal and Burned Tissues, *Ann. Int. Med.* **9**:850-853 (Jan.) 1936.

17. Fender, F. A.: Lymphatic Pathology in Relation to the "Toxin" of Burns, *Surg., Gynec. & Obst.* **57**:612-620 (Nov.) 1933.

18. Rosenthal, S. R.: The Toxin of Burns, *Ann. Surg.* **106**:111-117 (July) 1937.

of the uterus of the virgin guinea pig, which was present both in red blood cells and in serum and which was not histamine, although it resembled histamine in some respects.

Wilson and his associates⁹ carried out under strict aseptic precautions an ingeniously conceived and carefully controlled set of experiments with the edema fluid which accumulates at the site of burns. They produced such accumulations of fluid, without necrosis of the skin or injury to viscera, and later recovered the fluid and injected it into intact animals in various doses and at various intervals after the injury. For the first four hours this fluid, like the saline emulsions of normal skin, was harmless; thereafter it became progressively more toxic, and at forty-eight hours it was frequently lethal.

In this connection it is interesting to recall that Davidson's¹⁹ tannic acid treatment, probably the most widely used local measure available today, was developed on the basis of a presumptive toxin in burns. Mason,¹⁶ who made the suggestion to Davidson because he thought that deaths following burns, like death following the implantation of liver in the abdominal cavity,²⁰ might be due to tissue autolysis, believed that the absorption of toxins might be prevented by the use of tannic acid to precipitate the dead and dying tissues.

For a considerable period the contention of Underhill and his associates⁶ that hemoconcentration adequately explains the second, so-called toxic stage of burns was accepted, if for no other reason than that no proof was produced by which it could be overthrown. Such proof has recently been brought forward by Lucido²¹ and by Elkinton and his associates⁸ in the form of detailed case studies by which it has been possible to show that a true stage of toxemia, in some instances terminating fatally, can occur when the hemoconcentration and plasma loss supposedly responsible for it can be demonstrated, by laboratory tests, to have been present and to have been entirely corrected.

If these observations can be corroborated in an adequate number of cases, they are of extreme importance, because they prove certain facts: (1) that clinical toxemia can exist in the absence of hemoconcentration and plasma loss; (2) that there is nothing essentially incompatible between the antecedent existence of hemoconcentration and the subsequent development of toxemia; (3) that there is no real reason why

19. Davidson, E. C.: Tannic Acid in the Treatment of Burns, *Surg., Gynec. & Obst.* **41**:202-221 (Aug.) 1925.

20. Mason, E. C.: A Note on the Use of Heparin in Blood Transfusion, *J. Lab. & Clin. Med.* **10**:203-206 (Nov.) 1924. Mason, E. C., and Nau, C. A.: The Causes of Death Due to Liver Autolysis, *Surg., Gynec. & Obst.* **60**:769-774 (April) 1935.

21. Lucido, J.: Metabolic and Blood Chemical Changes in a Severe Burn, *Ann. Surg.* **111**:640-644 (April) 1940.

toxemia and hemoconcentration should not exist simultaneously if hemoconcentration has not been corrected before toxemia sets in and if it is not at such a level (between 125 and 140 per cent) as to threaten life.

THE HEPATIC FACTOR IN BURNS

A rather detailed discussion of the toxic theory of burns is a necessary preliminary to the discussion of the hepatic or hepatorenal factor in burns. It would be an oversimplification of the subject to say that an acceptance of the toxic theory of burns presumes the existence of a liver or liver-kidney lesion or that the existence of these lesions always implies the presence of clinical toxemia. It is fair to say, however, that these clinical and pathologic findings are associated in a large number of cases and that the clinical picture of toxemia in burned subjects bears a striking resemblance to the clinical picture in such definitely hepatic states as the so-called liver death or liver-kidney syndrome.

The opponents of the toxic theory of burns have been guilty of one curious omission. They have overlooked or otherwise failed to explain the hepatic lesion so frequently found in the postmortem examinations of burned patients. The omission is the more curious because Bardeen,²² in what is generally granted to be the classic description of the pathologic process in burns, put particular emphasis on it. In his study of 5 fatal cases of burns, in all of which death occurred promptly after injury, he pointed out that the chief changes noted at autopsy were focal degenerations in the lymphatic tissues and the liver and advanced parenchymatous degeneration of the kidneys. He himself was so impressed with the similarity of the observations in the 5 cases that he said that a single description could easily suffice for them all.

How little attention has been paid to this phase of the subject is illustrated by its treatment in the comprehensive monograph on burns by Pack and Davis.²³ The liver is dismissed with the statement that the toxin of burns is cytotoxic for parenchymal organs and that the characteristic hepatic change consists of hyperemia, focal necrosis and parenchymatous degenerative lesions. The discussion of the pathologic changes in the kidneys, which have been considerably less universally ignored, is far more complete.

Scanty as is the postmortem evidence, there is no doubt that the liver lesion actually exists. It was present in some of the cases in the

22. Bardeen, C. R.: *A Review of the Pathology of Superficial Burns, with a Contribution to Our Knowledge of the Pathological Changes in the Organs in Cases of Rapidly Fatal Burns*, Johns Hopkins Hosp. Rep. 7:137-179, 1899.

23. Pack, G. T., and Davis, A. G.: *Burns: Types, Pathology and Management*, Philadelphia, J. B. Lippincott Company, 1930.

Charity Hospital series in which postmortem examination was possible in the hospital laboratory, and it has been reported by McClure,²⁴ Elkin-ton,⁸ Belt²⁵ and Zinck,²⁶ as well as by Wilson and his associates⁹ in the most extensive and carefully recorded study of this type of burns.

The material studied by Wilson and his group consisted of 65 cases of serious burns, 23 of which were fatal and in 20 of which autopsy was permitted. To these 20 cases were added 13 others, in which less exhaustive studies had been made during life. In 14 of 16 cases in which clinical toxemia had been very severe, the liver had suffered intense damage, and milder degrees of damage could be correlated with less severe degrees of toxemia in a smaller number of cases.

Experimental studies also serve to corroborate the existence of a liver or a liver-kidney lesion in burns. As early as 1904 Parascandolo²⁷ had described fatty degeneration of the liver and the kidneys, presumably caused by a circulating toxin with a specific effect on these organs. The changes found by Robertson and Boyd¹² after the injection of extracts of burned skin and of blood from burned animals included cloudy swelling, fatty metamorphosis and parenchymatous degeneration of the liver and cloudy swelling of the kidneys.

In the experimental studies of edema fluid collected from the burned area carried out by Wilson and his associates,⁹ the liver was invariably the organ which had sustained the greatest damage, and the changes were invariably degenerative and necrotic in character. These authors expressed the belief that such changes, either clinically or experimentally, could not be produced by any agent other than a powerful toxin with an apparently specific action on the liver.

THE CLINICAL PICTURE OF TOXEMIA

The clinical picture of the so-called toxemia of burns is generally agreed on, even by those who decline to describe the syndrome as toxic. Symptoms may appear as early as six or eight hours after injury, though they more often occur between the third and fifth days or sometimes later. Shock is not necessarily an antecedent. The onset is usually insidious, and the syndrome often develops in a patient whose progress has been satisfactory or even good, and who has certainly given no cause for anxiety. For some inexplicable reason the toxemic state is rather more likely to be associated, particularly in its fatal form, with super-

24. McClure.¹ McClure and Lam.²

25. Belt, T. H.: Liver Necrosis Following Burns, Simulating the Lesions of Yellow Fever, *J. Path. & Bact.* **48**:493-498 (May) 1939.

26. Zinck, K. H.: Gestaltliche Leber-Nierenschädigungen und hepato-renale Insuffizienz nach Verbrennung: Ein Beitrag zur Frage des Verbrennungskollapses, *Klin. Wchnschr.* **19**:78-84 (Jan. 27) 1940.

27. Parascandolo, cited by Harkins.^{7a}

ficial and limited rather than with extensive burns (figs. 1 and 2). The Charity Hospital statistics are not unusual in this respect.

A change in the mental state is one of the first symptoms. The patient may become restless, irritable and apprehensive in turn. He is first drowsy and then comatose, or he may pass from disorientation into delirium, which may be extreme and which is always a bad sign, particularly if it comes on early. Convulsions are frequent in young children. The fever mounts rapidly, the temperature reaching 105 F. or higher, and the pulse and the respiration are correspondingly rapid, though the respiration is not otherwise altered. Vomiting is usually present. The skin and mucous membranes have a cyanotic or grayish tinge, the eyes are sunken and the pupils are dilated. In the fatal cases death is seldom long deferred.

The most obvious manifestation of the hepatic lesion is the development of jaundice. Pack and Davis²³ did not mention it as a possible complication of burns, but it was present in a number of cases in the Charity Hospital series and has been reported by McClure,¹ McClure and Lam,³ Zinck²⁶ and others who have paid special attention to this phase of burns.

Wilson and his associates⁹ regard jaundice not as a complication of burns but as an integral part of the pathologic process. It was present in 12 of the 65 cases of serious burns which they studied, and they observed, significantly, that the incidence would have been higher had they realized its significance and looked for it earlier in their study. It was not related to the presence of sepsis or to the mode of treatment but seemed a definite index of the degenerative and necrotic changes observed in the liver in the fatal cases in which autopsy was permitted.

Children and adolescents are peculiarly susceptible to this complication, and it is peculiarly fatal in these age groups (fig. 3). Wakeley²⁸ commented on the unusually low incidence of toxemia in the soldiers and sailors rescued from Dunkirk and on their excellent toleration of this stage, when it did develop, even though treatment was delayed and conditions were often unfavorable for recovery. He attributed this toleration to their good physical condition. There is another possible explanation, however, of the low incidence of toxemia and its low mortality in this particular group of patients. It is implicit in Wakeley's later statement²⁹ that in his opinion infection was the most frequent cause of toxemia in the more than 1,000 *war* (*italics mine*) burns which he treated. In other words, Wakeley was discussing bacterial toxemia and not the hepatic

28. Wakeley, C. P. G.: War Burns and Their Treatment, Practitioner **146**: 27-37 (Jan.) 1941.

29. Wakeley, C. P. G.: The Treatment of War Burns, Surgery **10**:207-232 (Aug.) 1941.

type of toxemia with which this paper is concerned, the incidence of which, as will be pointed out later, is never large, though the mortality is always high.

THE LABORATORY ASPECT OF THE HEPATIC FACTOR IN BURNS

It is not possible by any tests so far available to predict the development of toxemia in any given case, which is unfortunate, for once toxemia has fully developed, it is almost impossible to combat it. On the other hand, laboratory tests of hepatic function have supplied further evidence of the role of the liver in the toxemia of burns.

An elevated icteric index would, of course, be expected in the presence of jaundice, clinical or latent. The warning might profitably be issued, however, that jaundice does not always indicate hepatic damage; in some instances it may be of the hemolytic variety.

My own studies with the Quick hippuric acid test of liver function in burns, supplemented in a few cases with the serum bilirubin test, have been reported in detail elsewhere.³⁰ They are not numerous, but in practically every instance some degree of functional impairment was found, which was frequently, though not constantly, capable of rough correlation with the surface area and the depth of the lesion. These observations are in accord with those of others⁴¹ who have made such studies.

The carefully controlled cases reported by Wolff, Elkinton and Rhoads⁸ offer valuable corroborative evidence of the liver factor in burns. The disturbances of fluid balance were shown by laboratory evidence to have been corrected within forty-eight hours of the injury, yet the serum bilirubin, bromsulphalein, hippuric acid, plasma prothrombin and dextrose tolerance tests, all of which were carried out one or more times, showed at some time deviations from normal. In view of the number and variety of tests, the liver damage thus indicated can reasonably be accepted at its face value.

In a personal case, reported in detail elsewhere,³⁰ the initial value for the hippuric acid test was only 29.3 per cent of normal, though the burns were only of second degree and involved only 25 per cent of the body surface. Convalescence, although slow, was reasonably satisfactory, but only on one occasion did the serial tests of liver function by the Quick method rise above 60 per cent of normal. On the twenty-eighth day mesenteric thrombosis developed, for which extensive resection of the small bowel was done without undue delay or special difficulty. After a period of remarkably gratifying improvement the patient began

30. Boyce, F. F.: *The Rôle of the Liver in Surgery*, Springfield, Ill., Charles C. Thomas, Publisher, 1941.

31. McClure,¹ McClure and Lam,³ Zinck.²⁶

to do badly, and death occurred on the tenth postoperative day (the thirty-eighth day after the injury). The localized peritonitis found at autopsy was perhaps sufficient to explain the death, but not to be ignored were the marked degenerative changes found in the liver, which were in keeping with the constantly depressed hepatic function. The case is to be compared with the case reported by Wilson and his associates,⁹ in which postmortem examination of a patient who died of accidental causes fourteen days after a burn revealed intense necrotic changes in the liver.

PATHOLOGIC ASPECTS OF THE LIVER LESION

Wilson and his associates⁹ have provided the most detailed description of the liver lesion in burns. It was not present in any of their cases in which death occurred earlier than twenty-one hours after injury, though I have personally observed it as early as eight hours (fig. 4). From twenty-one to fifty-seven hours, the characteristic change, which was discernible only by the microscope, consisted of fatty metamorphosis of the epithelial cells surrounding the efferent veins in the central zone of the hepatic lobules, accompanied by nuclear damage, especially karyolysis.

From fifty-seven hours onward, gross changes were evident to the naked eye. The liver was slightly enlarged, light yellow, soft, greasy and friable. On section, the central zone, although usually pallid, was sometimes hemorrhagic, and the liver was of the nutmeg variety. Microscopic study, in the light of microscopic studies in earlier fatal cases, made it clear that the underlying pathologic process was essentially a degeneration leading to necrosis of the parenchymal cells. Definite signs of severe bacterial infection were observed in 8 of 13 cases in which death was deferred, sometimes as long as six weeks after injury, but typical liver lesions were found in the remaining cases.

In the extent and completeness of destruction of hepatic tissue, Wilson and his associates pointed out, the microscopic picture was comparable with that of acute yellow atrophy of the liver, differing only in the constant, characteristic zonal distribution. In their opinion, "the liver lesion furnished the strongest indication of a non-bacterial toxin circulating during the first few days after a burn." They added that in the extensive studies which they carried out they were never able to associate the development of toxemia with hemoconcentration per se, with the growth of any type of organism in the burned area, with the changes in blood chemistry frequently though not constantly present in burns or with any other cause except the liver lesion described. Elkinton² also made the point that the liver lesion of burns is not associated with the acute visceral congestion and hemorrhage typically present in patients dying of hemoconcentration.

Wilson and his associates pointed out that the hepatic lesion of burns differs from a lesion of bacterial origin in that the central rather than the peripheral zone is affected and that the liver cell injury is far more pronounced.

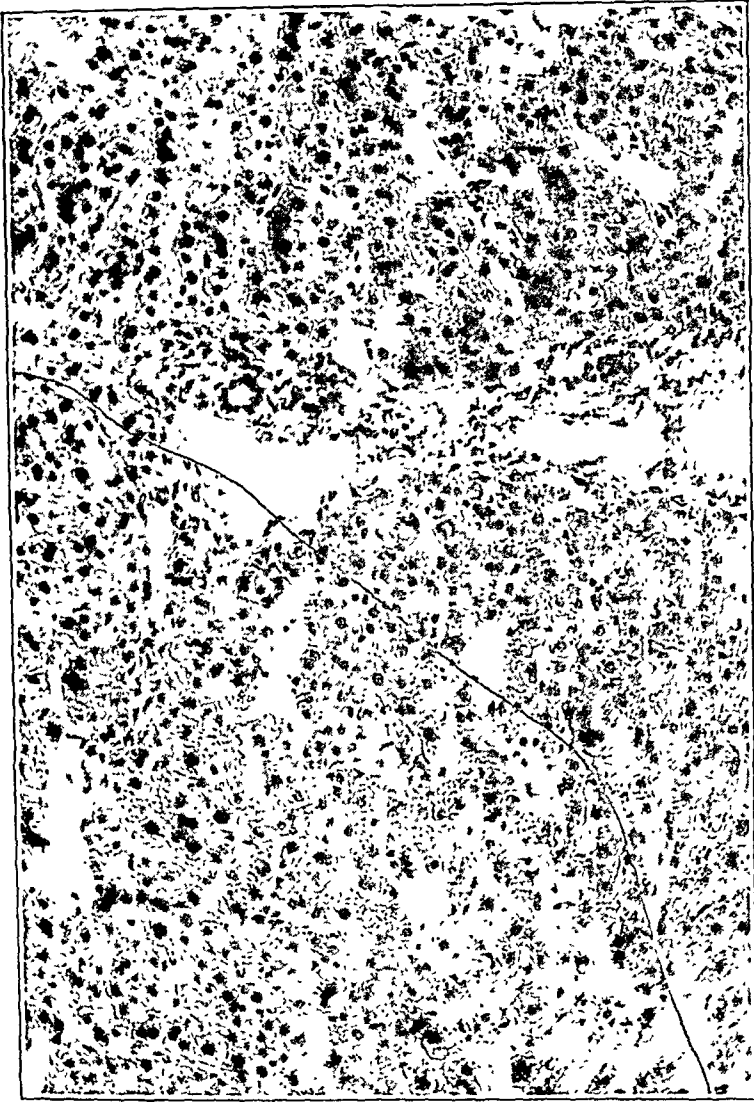


Fig. 4.—Photomicrograph ($\times 192.3$) of the liver showing hyperemia, cloudy swelling and slight lymphocytic infiltration of periportal tissue in a case of third degree burns in which death occurred in seven hours.

In 4 of the 5 cases studied in detail by Buis and Hartman³² the postmortem observations were similar to those described by Wilson and his associates. Midzonal necrosis was also a characteristic feature in the

32. Buis, I. J., and Hartman, F. W.: Histopathology of the Liver Following Superficial Burns, *Am. J. Clin. Path.* **11**:275-287 (April) 1941.

4 cases studied intensively by Belt,²⁵ who pointed out the similarity of the hepatic lesion in burns and in yellow fever.

On the other hand, extreme changes are by no means always the rule, nor is necrosis the only type of hepatic lesion found. Eppinger³³ mentioned serous inflammation of the liver, and Keschner and Klemperer³⁴ commented on the relatively high incidence of hepatic edema in burns. In many instances cloudy swelling (fig. 4) or fatty metamorphosis (fig. 5) is the chief hepatic change.

Zinck²⁶ attributed the lobular necrosis of the liver observed in many of his own cases to the state of the capillaries, which in turn he attributed to the action of protein degradation products from the burned area. This explanation, in one form or another, underlies the whole theory of the toxemia of burns, though certain other causes may also play a part.

It is quite possible that anoxia is responsible for part of the picture. It is one of the phases of the stage of hemoconcentration, and lack of oxygen has been clearly shown by Hawkins,³⁵ Judd, Snell and Hoerner³⁶ and Ravdin and his associates³⁷ to have a distinctly adverse effect on the liver.

Fatty metamorphosis is open to two possible explanations. It may be the result of hyperglycemia, which is part of the first stage of burns and which is associated with a prompt loss of glycogen from the liver and other tissues. It may also be due to the protein loss associated with plasma loss. As Ravdin³⁸ has demonstrated, protein deficiency leads to an excessively high lipid content in the liver.

Pierre Duval,³⁹ who believes that autolyzing tissue at the site of the burn acts as a toxin, has suggested that repeated burns may so sensitize an animal as ultimately to confer a certain immunity or resistance to this type of injury. In the same connection, Wilson and his associates⁹ have suggested anaphylaxis as a possible explanation of the occasional

33. Eppinger, cited by Zinck.²⁶

34. Keschner, H. W., and Klemperer, P.: The Frequency and Significance of Hepatic Edema, *Arch. Path.* **22**:583-592 (Nov.) 1936.

35. Hawkins, J. A.: Acceleration of Blood Coagulation by Breathing Oxygen, *Proc. Soc. Exper. Biol. & Med.* **31**:1095 (June) 1934.

36. Judd, E. S.; Snell, A. M., and Hoerner, M. T.: Transfusion for Jaundiced Patients, *J. A. M. A.* **105**:1653-1658 (Nov. 23) 1935.

37. Goldschmidt, S.; Ravdin, I. S., and Lucké, B.: Anesthesia and Liver Damage: I. The Protective Action of Oxygen Against the Necrotizing Effect of Certain Anesthetics on the Liver, *J. Pharmacol. & Exper. Therap.* **59**:1-14 (Jan.) 1937. Ravdin, I. S.; Vars, H. M.; Goldschmidt, S., and Klingensmith, L. E.: Anesthesia and Liver Damage: II. The Effect of Anesthesia on Blood Sugar, the Liver Glycogen, and Liver Fat, *ibid.* **64**:111-129 (Sept.) 1938.

38. Ravdin, I. S.: Some Recent Advances in Surgical Therapeutics, *Ann. Surg.* **109**:321-333 (March) 1939.

39. Duval, P., cited by Rudler, J.: Etat actuel du traitement des brûlures superficielles en pratique courante, *Bull. méd., Paris* **49**:343-347 (May 18) 1935.

deaths which occur promptly after burns not of sufficient severity to account for the fatality. In support of their argument they cited the case of a patient who had sustained a burn a year prior to the second burn, from which he died in twenty-four hours, though it involved only 5 per cent of the body surface.



Fig. 5.—Photomicrograph ($\times 192.3$) of the liver showing marked fatty metamorphosis in a case of first and second degree burns, in which the liver-kidney type of death occurred in five days. Compare with the kidney shown in figure 6.

When tests of liver function are employed to demonstrate a possible hepatic factor in burns, it must not be forgotten, particularly in older patients, that a demonstrable depression may possibly be due, at least in part, to preexistent hepatic damage. I have set forth elsewhere³⁰ my own view and the views of others on the "liver weakling," and the

theory really strengthens the case for the liver factor in burns, since a subject whose liver is already damaged would seem peculiarly liable to the prompt development of additional hepatic damage.

THE RENAL (HEPATORENAL) FACTOR IN BURNS

That the renal lesion in burns should have been recognized for many years is not surprising, since albuminuria and hematuria are rather frequent findings, and oliguria and even anuria are not really uncommon. Changes in the chemistry of the blood may include large increases in nonprotein nitrogen and slighter increases in the urea. It is difficult to evaluate the so-called residual nitrogen, on which Zinck²⁰ and other German investigators lay such stress, since it is not usually determined in American laboratories.

These findings are usually explained either as the direct result of the burn on the kidney or as due to a diminution in the ability of the kidneys to excrete toxic degradation products because of loss of chlorides into the tissues, both from the burned area and as the result of vomiting. Both of these explanations are probably correct. They do not, however, cover such cases as have been reported by Lucido²¹ and by Zinck²⁰ or as I myself have observed,³⁰ in which uremic manifestations are present without any laboratory evidence of renal insufficiency.

Cases of this type can readily be explained by the concept that uremic manifestations and alterations in kidney function and blood chemistry are not always an index of renal insufficiency per se but are rather a reflection of liver damage and of its effect on the kidney. This theory is in accord with the suggestion of Wilensky and Colp¹⁰ in 1927, that chemical tests of renal function are useful as indexes of liver function. Elsewhere³⁰ I have cited both clinical and experimental evidence to show that efficient kidney function is at least partially dependent on and maintained by efficient liver function. Nonnenbruch⁴¹ suggested that liver damage may be so great in some cases as to result in complete failure of the function of urea formation.

This explanation of the renal factor in burns leads directly to the parallel between this type of injury and the so-called liver death and liver-kidney syndrome. Deaths which occur promptly after burns, with hyperpyrexia and hepatic necrosis as the outstanding features, correspond to the so-called liver death. Deferred deaths, in which the renal factor is outstanding and postmortem examination reveals pathologic changes

40. Wilensky, A., and Colp, R.: Relation of Nitrogen Bodies of the Blood to Surgical Problems in Liver and Biliary Tract Disease: III. Status of Nitrogen Bodies of Blood in Severe Cases of Biliary Tract Disease and Its Use in Differentiating a Terminal Hepatic and a Terminal Renal Group of Cases, *Arch. Surg.* **15**:635-659 (Oct.) 1927.

41. Nonnenbruch, cited by Zinck.²⁰

in both the liver (fig. 5) and the convoluted tubules of the kidney (fig. 6), correspond to the so-called liver-kidney syndrome.

The parallel is both clinical and pathologic. It therefore does not seem unreasonable to explain certain deaths after burns on the same basis as so-called liver or liver-kidney deaths. Briefly, the liver finally

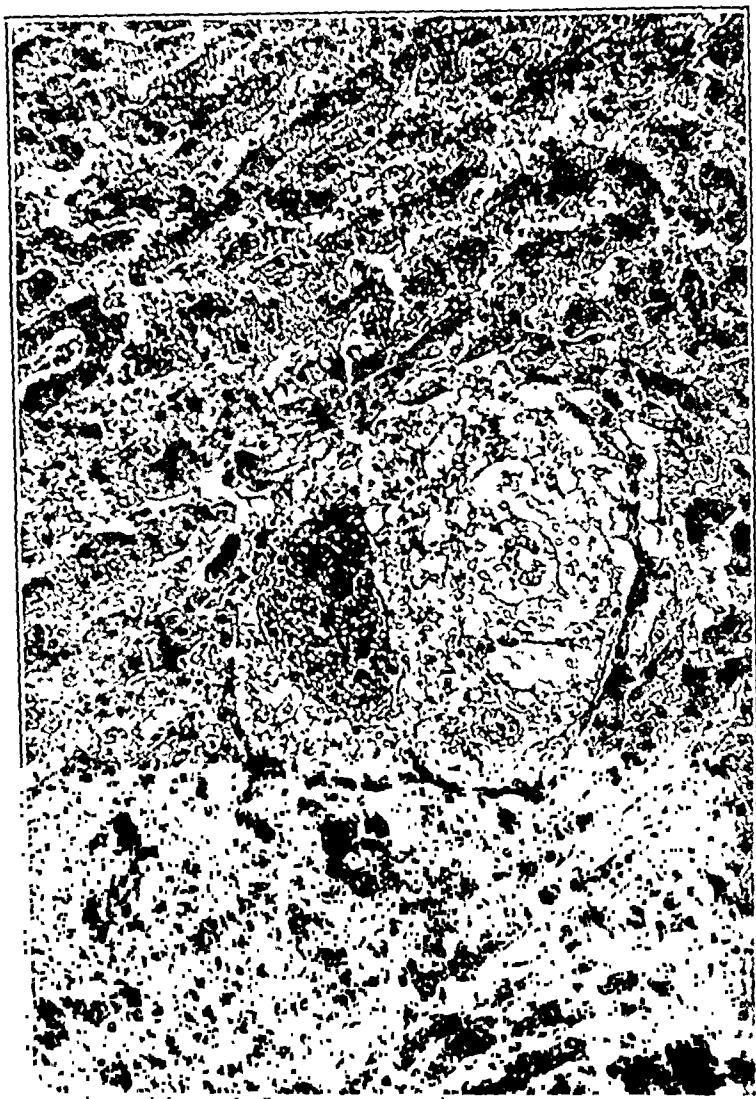


Fig. 6.—Photomicrograph of a kidney showing marked degenerative changes in the tubular epithelium and intraglomerular hemorrhage in a case of first and second degree burns, in which the liver-kidney type of death occurred in five days. Compare with the liver shown in figure 5.

fails in its function of detoxification because it is completely overwhelmed by the toxins poured out into the circulation from the burned surface. If the patient lives long enough, the kidney is overwhelmed in its turn. It is the second great organ of detoxification in the body, and when liver

function fails it takes on a hyperfunction utterly beyond its ability to carry on for any sustained period.

THE INCIDENCE OF TOXEMIA IN BURNS

It should not be assumed, from what has been said, that well marked toxemia is an inevitable or even an especially frequent development in the usual run of unselected burned patients. The series reported by Wilson and his associates⁹ is not in the least typical. It consisted of cases selected frankly because the condition was serious or was likely to be.

A careful analysis of the 1,243 burns treated at Charity Hospital in the period specified is proof of the relative infrequency of toxemia of

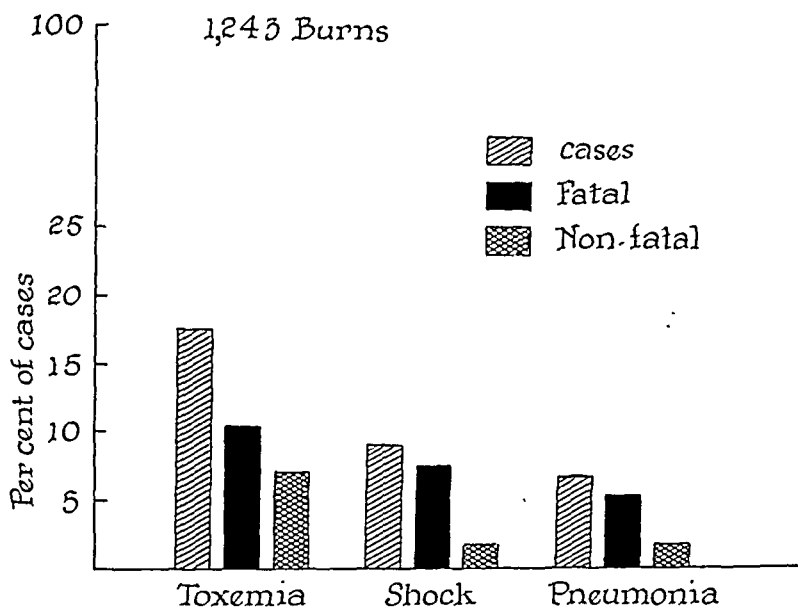


Fig. 7.—Distribution of certain complications and causes of death in 1,243 burns, 217 of which were fatal. The figures for the various groups are overlapping.

any degree both in fatal and in nonfatal cases (fig. 7). Toxemia of all degrees played a part in more cases than either shock or pneumonia, but toxemia of extreme degree was relatively infrequent; this is shown by the number of fatal cases in which, either alone or in combination, it played any part (fig. 1). It is doubtful whether it would play a greater average role in any other unselected series of burns of all degrees of extent and depth.

THERAPEUTIC CONSIDERATIONS RELATED TO THE HEPATIC FACTOR IN BURNS

Although a discussion of therapy forms no part of a paper such as this, certain general principles of treatment are related to the phase of the subject under discussion. An institution which undertakes the

treatment of so serious a condition as burns should have a definite therapeutic regimen, no detail of which should be left to chance and which should have as its point of departure the concept that the patient's general condition is more important than his local condition.

From the standpoint of the hepatic or toxemic factor, however, local measures are not unimportant. Advocates of the toxemic theory are in rather general agreement that acute toxemia can be minimized by adequate local measures, including the use of a tanning agent. Even Dunbar,⁵ who cannot bring himself to believe that toxemia is due to absorption from breaking down proteins, has granted that if the traumatized area is kept sterile this clinical stage is less likely to develop.

The restoration of the disordered fluid balance is not directly related to the liver factor except that the administration of plasma is helpful in respect to the liver, in view of Ravdin's³⁸ demonstration that fatty metamorphosis is decreased or prevented by the use of a high protein intake. Plasma should be administered on a strictly calculated basis, both as to the amount needed and as to the period of administration. The formula proposed by Harkins⁴² for this purpose, because of its simplicity, is generally applicable.

Administration of dextrose must be carried out if the theory of hepatic damage is accepted, but the promiscuous giving of fluids is never warranted. If dextrose can be given by mouth, the risk of excessive fluid administration is avoided. Althausen⁴³ has demonstrated the effectiveness of the oral route, and my own studies³⁰ with the Quick hippuric acid test of liver function corroborate his evidence. Seriously ill patients, however, who need carbohydrates most of all, are likely to be vomiting, and dextrose must be given by infusions; these should be given very slowly and on the basis of the patient's calculated needs.

Certain other therapeutic measures should be reevaluated in the light of their possible effect on the liver. Thus Elman's⁴⁴ suggestion that in an emergency, while plasma is being secured and prepared, a single administration of gum acacia is useful, since this agent has proved colloidal properties, is accompanied by the warning that its deleterious effects on the liver also have been proved.

Anesthesia for preliminary débridement and cleansing should be avoided whenever possible, not only because it is undesirable in a shocked subject, but in view of my own demonstration,³⁰ which confirms the

42. Harkins, H. N.: The Treatment of Burns with Particular Emphasis on the Management of Burn Shock, Brochure prepared in connection with Exhibit on Burn Shock, Meeting of American Medical Association, Cleveland, June 2-6, 1941.

43. Althausen, T. L.: Dextrose Therapy in Diseases of the Liver, *J. A. M. A.* **100**:1163-1167 (April 15) 1933.

44. Elman, R.: The Therapeutic Significance of Plasma Protein Replacement in Severe Burns, *J. A. M. A.* **116**:213-216 (Jan. 18) 1941.

work of others,⁴⁵ that a depression of liver function accompanies any type of anesthesia, even in normal subjects. A patient given proper sedation can usually be treated without anesthesia.

Finally, sulfanilamide and its derivatives, which have been used for some time in infected burns and the wider use of which is now being advocated, should be employed with caution. My own evidence³⁰ corroborates the evidence of others⁴⁶ that these drugs may have a damaging effect on the liver, and these effects are likely to be enhanced if the drugs are used without due precautions for patients whose livers are already damaged by the toxins of burns.

SUMMARY AND CONCLUSIONS

Although the universal application of the theory of hemoconcentration in burns is granted, it is pointed out that considerable valid evidence also exists in favor of the toxemic theory, and it is suggested that the two theories are not mutually exclusive.

The hepatic factor in the nonbacterial toxemia of burns is discussed from the experimental, clinical, laboratory and pathologic (postmortem) aspects.

The renal lesion in burns is considered as a secondary phase of the hepatic lesion, and a parallel is traced between certain deaths from burns and the so-called liver death and liver-kidney syndrome.

It is pointed out that well marked toxemia plays a part in only a small proportion of burns, whether fatal or nonfatal.

The therapy of burns is discussed in its relation to the liver factor.

A certain mortality is probably inevitable with burns. Generally speaking, persons who are burned extensively are unlikely to recover, regardless of the method of treatment employed, while at the other extreme patients who are slightly burned are likely to recover, though certain entirely unexpected deaths may occur in this group. The patients who provide these unexpected fatalities and the patients in the middle group, who may or may not recover and whose chances of life are chiefly dependent on how they are treated, offer the greatest opportunities for improvement in the present unhappy mortality from burns.

Attention to the hepatic and hepatorenal aspects of this type of injury is therefore suggested as one possible method of achieving this improvement.

45. Bourne, W.: Anesthetics and Liver Function, *Am. J. Surg.* **34**:486-495 (Dec.) 1936. Coleman, F. P.: The Effect of Anesthesia on Hepatic Function, *Surgery* **3**:87-99 (Jan.) 1938.

46. Watson, C. J., and Spink, W. W.: Effect of Sulfanilamide and Sulfapyridine on Hemoglobin Metabolism and Hepatic Function, *Arch. Int. Med.* **65**:825-846 (April) 1940.

SULFATHIAZOLE OINTMENT IN THE TREATMENT OF BURNS

J. GARROTT ALLEN, M.D.

FREDERICK M. OWENS JR., M.D.

BYRON H. EVANS, M.D.

AND

LESTER R. DRAGSTEDT, M.D.

CHICAGO

The treatment of burns in war injuries has brought out important points not hitherto well recognized. First, it has been found that the tannic acid treatment is not so satisfactory as is commonly stated.¹ Second, the life-saving value of plasma replacement has been satisfactorily demonstrated. In the light of this knowledge, a variation of the treatment of severe burns is here presented.

With the introduction of the tannic acid treatment of burns by Davidson in 1925,² there was a sharp decline in the mortality and morbidity rates associated with severe burns. Subsequently, many variations of the method were employed. Most of these were aimed in particular at tanning the burned area, although dyes which combined tanning action with bacteriostasis were widely employed.

In 1925, Davidson² advocated the application of 2.5 per cent solution of tannic acid to produce a tough membrane over the burned areas. The design was to prevent the loss of fluid and protect the raw surface against infection. It was found that infection readily developed beneath the eschar and that there was much scarring in the areas to which the tannic acid was applied. It is widely held also that the tannic acid eschar destroys small islands of epithelium which were not completely destroyed by the thermal injury.

In 1929, Firor and Aldrich³ introduced the gentian violet treatment. They suggested that the toxemia of burns arises from infection. They therefore employed a bacteriostatic agent, namely, gentian violet, in their

From the Department of Surgery, the University of Chicago.

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1. Mowlem, R.: The Treatment of Burns, *Proc. Roy. Soc. Med.* **34**:221, 1941.

2. Davidson, E. C.: The Tannic Acid Treatment of Burns, *Surg., Gynec. & Obst.* **41**:202, 1925.

3. Aldrich, R. H.: The Story of Burns, *New England J. Med.* **208**:299 (Feb. 9) 1933.

therapy. Finding that the gentian violet inhibited only the gram-positive organisms, Aldrich,⁴ in 1933, added brilliant green and neutral acriflavine to the gentian violet and found more effective bacteriostasis resulting therefrom. The dyes have been found to be far more effective than tannic acid in the prevention of infection, and they have an additional advantage of producing a light tough flexible eschar in contrast to the heavy rigid tannic acid eschar.

Other procedures, such as pressure saline dressings, saline baths,⁵ silver nitrate and cod liver oil,⁶ have been used and modified extensively, but with such excellent treatises on the subject of burns as Harkins' "Treatment of Burns"⁷ it is superfluous even to enumerate the various types of treatment.

With the increasing use of sulfanilamide and its derivatives in infections of various sorts, it is not surprising to find these drugs taking a place in the therapy of burns. In 1941, Pickrell⁸ reported a series of cases in which burns were treated with 3 per cent solution of sulfadiazine (2-[paraaminobenzenesulfonamido]-pyrimidine) in 8 per cent solution of triethanolamine. Unusual in his treatment is the fact that the burned areas are not washed. Débridement is effected, and sulfadiazine is then sprayed over the burned area. This forms a thin transparent membrane over the surface and is an effective bacteriostatic. Absorption of the drug was rapid at the onset but ceased when the eschar formed. In none of Pickrell's cases did the drug reach toxic levels in the blood.

Hooker and Lam⁹ reported 8 cases of burns treated with powdered sulfanilamide. In 5 of these cases, blood concentrations of from 1.0 to 4.5 mg. per hundred cubic centimeters were obtained. In 3 cases, significantly higher levels were obtained as follows:

- From a burn measuring 15 by 4 cm., 9.4 mg. per hundred cubic centimeters
- From a burn measuring 8 by 6 cm., 7.8 mg. per hundred cubic centimeters
- From a burn measuring 30 by 60 cm., 33.0 mg. per hundred cubic centimeters

Although the significance of hemoconcentration in severe burns has been long recognized, it was not until 1936 that the full importance of

4. Aldrich, R. H.: The Role of Infection in Burns with Special Reference to Gentian Violet, *New England J. Med.* **208**:299, 1933.

5. Blair, V. P.; Brown, J. B., and Hamm, W. J.: The Early Care of Burns and the Repair of Their Defects, *J. A. M. A.* **98**:1355 (April 16) 1932.

6. Hardin, P. C.: The Cod Liver Oil Treatment of Burns, *North Carolina M. J.* **1**:82, 1940.

7. Harkins, H. N.: *The Treatment of Burns*, Springfield, Ill., Charles C. Thomas, Publisher, 1942.

8. Pickrell, K. L.: A New Treatment for Burns, *Bull. Johns Hopkins Hosp.* **69**:217, 1941.

9. Hooker, D. H., and Lam, C. R.: Absorption of Sulfanilamide from Burned Surfaces, *Surgery* **9**:534, 1941.

plasma loss was revealed by Weiner, Rowlette and Elman.¹⁰ Previously, the local treatment of the burned areas was of primary concern to the clinicians. But with the advent of plasma banks, the role of fluid balance in cases of burns has become more fully appreciated and is now being placed in its proper light.

Many studies have been made concerning the fluid shifts which occur in burned areas. Suffice it to say that Davidson and Matthew¹¹ in 1927 showed that the fluid lost from the burned areas was plasma. Others have confirmed this. Underhill, Kapsinow and Fisk¹² demonstrated that the fluid loss occurred by way of damaged capillaries in the burned area. This fluid loss occurred primarily into the tissues and not externally. That this is the case has been effectively demonstrated by Elkinton, Wolff and Lee¹³ in a study of 9 clinical cases of burns. They demonstrated that plasma restored the circulating blood volume but that physiologic solution of sodium chloride was ineffective in this respect.

From previous studies, therefore, it has become evident that replacement of plasma is the most important consideration in cases in which extensive tissue damage has permitted the escape of this portion of the blood. Physiologic solution of sodium chloride is unable to effect any lasting reduction of hemoconcentration. It merely increases the local tissue edema and augments hypoproteinemia by washing the plasma proteins out into the tissues. Oral ingestion of large amounts of water may lead to depletion of tissue electrolytes. Harkins⁷ compounded a rule which is an effective guide to the administration of plasma. He advocated the use of 100 cc. of plasma for every 1 per cent rise in the hematocrit reading above the normal of 44 per cent. This rule does not take into account the existing level of the plasma proteins, whereas Elkinton, Wolff and Lee¹³ devised a method for the direct determination of plasma requirement by means of a formula using the body weight, the plasma protein level and the hematocrit determination. Their formula for the calculation of plasma protein deficit is as follows:

$$\text{Plasma protein deficit in grams} = 3.5W - \frac{W(100 - H_o)H_nP_o}{2(100 - H_n)H_o}$$

In this formula W is the normal body weight; H_n , the normal hematocrit reading; H_o , the observed hematocrit reading, and P_o , the observed plasma protein concentration.

10. Weiner, D. O.; Rowlette, A. P., and Elman, R.: The Significance of Serum Protein in Therapy of Severe Burns, *Proc. Soc. Exper. Biol. & Med.* **34**:484, 1936.

11. Davidson, E. C., and Matthew, C. W.: Plasma Proteins in Cutaneous Burns, *Arch. Surg.* **15**:265 (Aug.) 1927.

12. Underhill, F. P.; Kapsinow, R., and Fisk, M. E.: Studies on the Mechanism of Water Exchange in Animal Organism, *Am. J. Physiol.* **95**:315, 325, 334 and 339, 1930.

13. Elkinton, J. R.; Wolff, W. A., and Lee, W. E.: Plasma Transfusion in the Treatment of the Fluid Shift in Severe Burns, *Ann. Surg.* **112**:150, 1940.

In general two simple clinical tests—the plasma protein content of the blood and the hematocrit reading—are invaluable in the management of plasma therapy in cases of severe burns. The degree of hemoconcentration can readily be followed by frequent determinations of the cell volume. Since the cell volume is *not* an index of plasma protein loss but merely of hemoconcentration, it is evident that determination of the plasma protein level is necessary as a guide to plasma replacement.

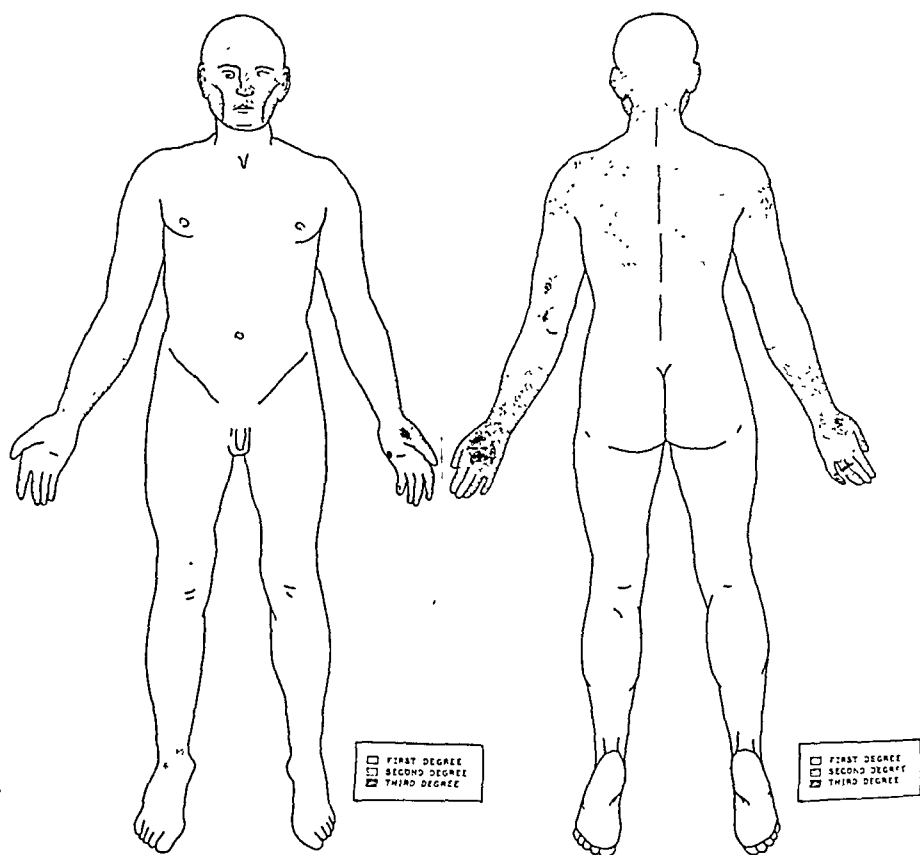


Fig. 1.—Extent of burns in patient H. G. The burned area was estimated at 27 per cent of the body surface.

Four patients were admitted to the Albert Merritt Billings Hospital on Oct. 27, 1941, fifteen minutes after an explosion and a fire in a chemical laboratory. The therapy employed is presented from the records of the 2 most severely burned patients. The illustrations reveal the extent and the nature of the burns and the fluid exchange and the blood findings observed in each case.

H. G., and E. O., healthy white men of 20 and 28 years of age, respectively, had extensive first, second and third degree burns about the face, the neck, the

hands, the arms and the back (figs. 1 and 2). The estimated burned surface area was 27 per cent on H. G. and 30 per cent on E. O. General physical examination was otherwise essentially negative. Morphine was given to each patient, and the clothing was removed. Intravenous administration of solution of sodium chloride was started, and the burned areas were débrided, cleansed with soap and water and copious amounts of physiologic solution of sodium chloride. After the injured parts were cleansed, they were dressed with sterile gauze heavily impregnated with 20 per cent solution of sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) in an oxycholesterol-petrolatum base. The patients were then placed on

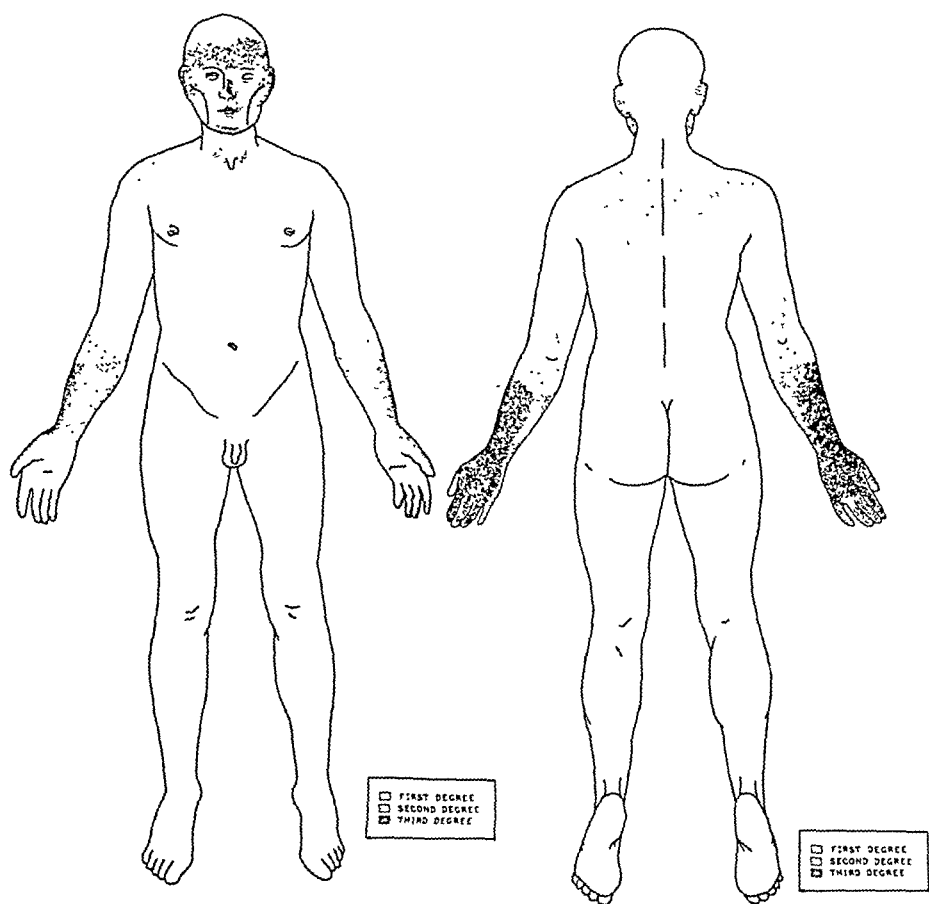


Fig. 2.—Extent of burns in the case of E. O. The burned area was estimated at 30 per cent of the body surface.

sterile sheets beneath heat cradles, and the intravenous administration of plasma was started. Within forty-five minutes to one hour following the application of the sulfathiazole ointment, the patients were free from pain.

Ten hours after the accident, E. O. complained of a dull aching pain in the midepigastrium, and a short time later he became nauseated and vomited 200 cc. of grossly bloody vomitus which was strongly acid. At this time a Levine tube was introduced into the stomach, and continuous aspiration was effected by means of a Wangenstein suction apparatus. Much relief was afforded the patient by this procedure, but because of the severe burns about the nostrils, the nasal tube

could be left in place for only a few hours at a time. Both patients were then submitted to modified ulcer management under which they remained for the first two weeks of hospitalization.

The following day, October 28, the sulfathiazole dressings of 1 patient (E O.) were replaced with wet saline packs for a period of four hours, and then the

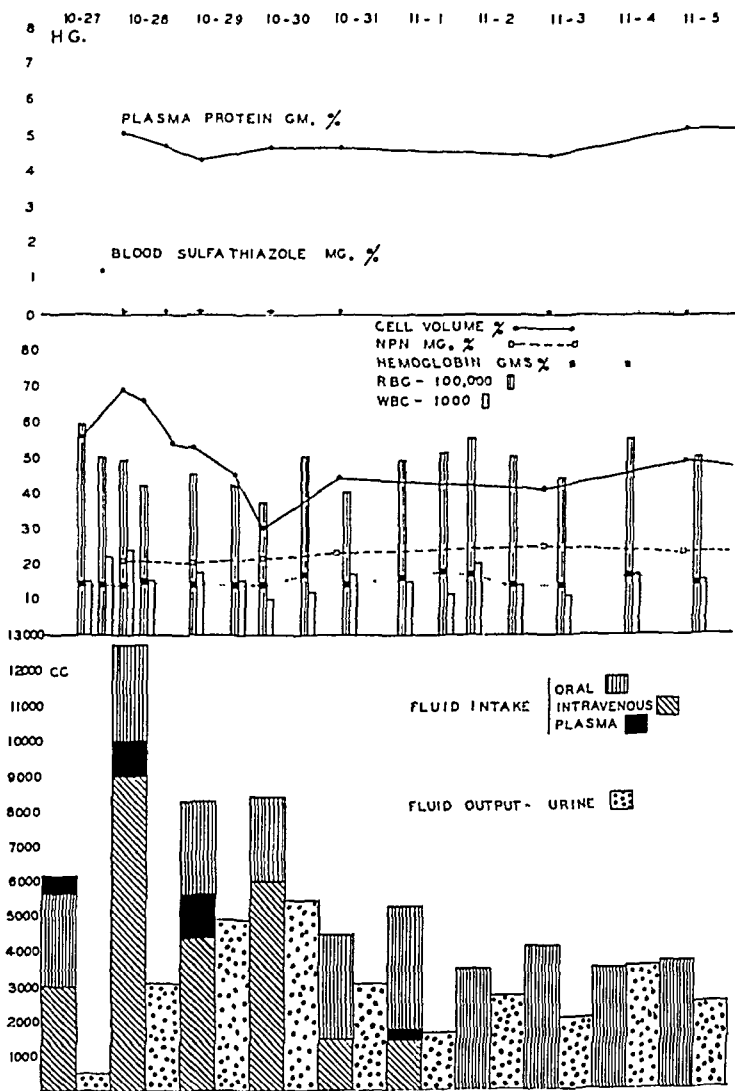


Fig. 3.—Chart of fluid exchange and variation of blood values in patient H. G.

ointment was reapplied. For four hours each day saline dressings were applied, but during the remainder of the time ointment dressings were in use. After the tenth day, continuous saline dressings were applied for the purpose of preparing the injured areas for grafting. Sulfathiazole dressings alone were employed on the other patient (H. G.) until the fourth day, when saline packs were applied as in the other case. Cultures taken from the burned areas of E. O. on the fifth day

yielded a growth of *Staphylococcus albus*, while it was not until the seventh day that positive cultures of the same organism were obtained from H. G. After four weeks, the dorsal surfaces of the forearms of E. O. were grafted with dermatome grafts, and a similar graft was placed on the dorsum of the left hand of H. G.

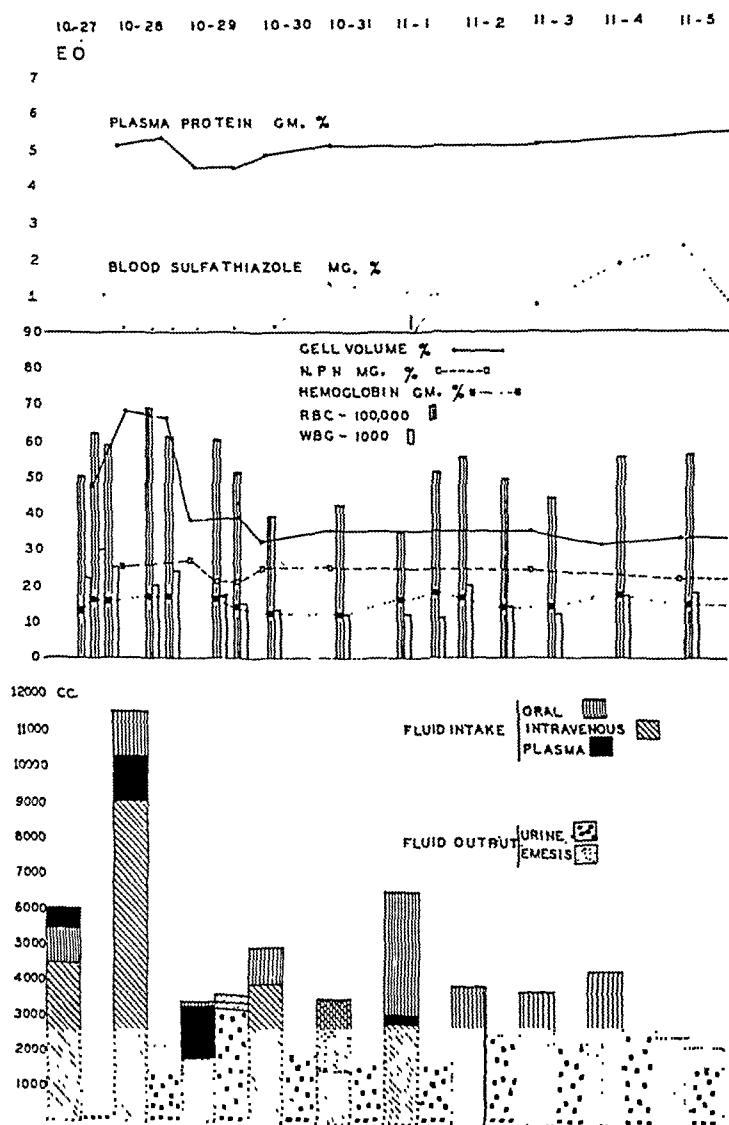


Fig. 4.—Chart of fluid exchange and variation of blood values in patient E. O.

The management of the fluid balance of these 2 patients is fully presented in figures 3 and 4. In retrospect, we must say that much larger volumes of plasma might well have been given during the first three days and considerably less solution of dextrose and sodium chloride. The high hematocrit values and the low plasma protein levels reveal that there was serious hemoconcentration and hypoproteinemia. Local tissue edema was extensive, suggesting that there was

not sufficient plasma protein osmotic pressure to retain the crystalloids in the circulating blood.

Recovery was remarkably rapid, and scarring was minimal. At the time of writing, the function of the hands is excellent, and although the fingers were severely burned, there is nowhere scar tissue contracture or limitation of motion.

The treatment here presented is of interest in that it sheds light on the benefits to be expected from the local use of sulfathiazole ointment in the therapy of thermal injuries. Pain is promptly alleviated. This was strikingly brought out by the fact that the patients pleaded for the return of the ointment following three or four hours of saline dressings. Infection is minimized, and scarring is apparently less severe. It is our feeling that remaining islands of epithelium are preserved and possibly even stimulated by the application of this chemotherapeutic agent.

Generally speaking, it is impossible to maintain a large denuded area in a sterile condition by the use of simple pressure dressings. Some bacteriostatic material is needed to maintain an aseptic field. This is particularly true in wartime, when a large number of patients must be treated by a small staff. With this consideration in mind, we propose the use of sulfanilamide and its derivatives in ointment form because of the bacteriostatic and analgesic effects of such a combination of chemotherapeutic agents.

Plasma loss may be minimized by the application of pressure dressings to the surfaces. Likewise, such dressings prevent to a considerable degree the edema accompanying such injuries as extensive burns. Coagulation of the weeping surfaces also has been successful in reducing the plasma loss. However, pressure dressings are probably more desirable than coagulation of the burned area, for the reported experience with the coagulative methods suggests that much of the epithelium which would ordinarily survive is probably killed as a direct result of the tanning agent used. Furthermore, tanning fixes the viable tissues on the surface of the denuded areas, thus leading to somewhat more extensive scarring than would otherwise result.

Since June 1941, we have been employing a 20 per cent sulfathiazole ointment. Sulfathiazole was chosen as the chemotherapeutic agent because its range of effective bacteriostasis is wider than that of any of the other three sulfanilamide drugs currently employed. Of particular importance is its effectiveness against the common pathogens. The most desirable concentration for such an agent is as yet undetermined, but we have found that an ointment containing 20 per cent of sulfathiazole gives rise to no grossly harmful effects. The photograph of the burned areas (fig. 5) taken fifteen days after the time of injury discloses numerous islets of epithelial regeneration in the areas subjected to this ointment almost continuously for two weeks. Likewise, when this ointment is

placed on the donor site of a dermatome graft no evident retardation of epithelial regeneration has been noted.

In the choice of an ointment base three features were considered desirable. First, the base itself should be nontoxic. We chose one (aquaphor) that contains 5 per cent oxycholesterol (a substance contained in human sebum) and 95 per cent petrolatum. Second, it seemed advisable that an absorbent base should be employed, since such a base theoretically tends to minimize the absorption of the drug by the tissues. Third, the ointment base should permit intimate contact between the sulfathiazole and the local tissues. An oxycholesterol-petrolatum base, more than petrolatum alone, affords this characteristic because of its

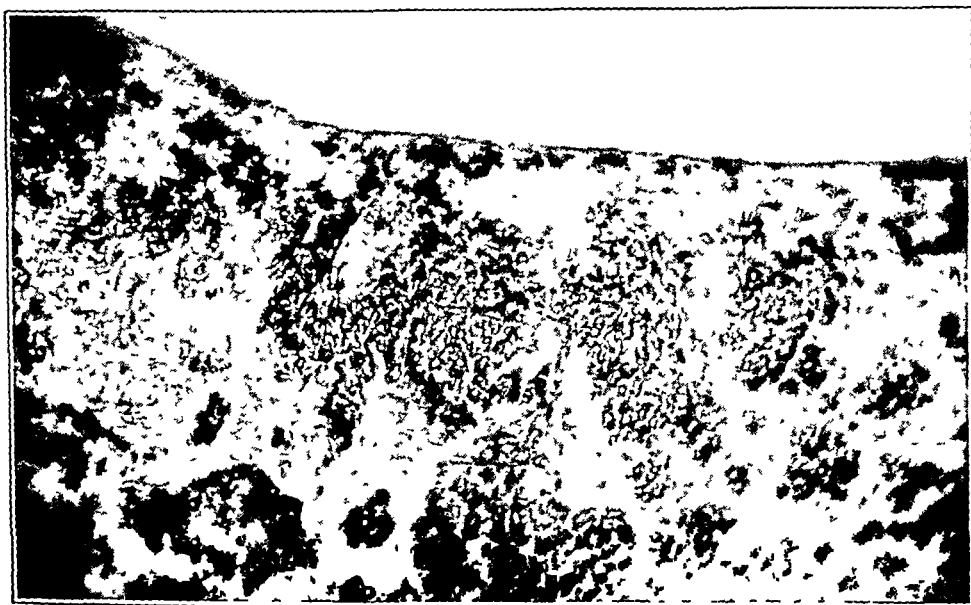


Fig. 5—Photograph of healing surface of third degree burn taken fifteen days after injury.

hydroscopic nature. By fulfilling these requirements such a base seems to be suitable as an ointment base for sulfathiazole.

Absorption of sulfathiazole from the extensively burned areas in these 2 cases was minimal. Daily collection of urine failed to disclose excretion of more than 2.0 Gm. per twenty-four hours in 1 case (E. O.) and 1.5 Gm. per twenty-four hours in the other case (H. G.). Likewise, the total sulfathiazole in the circulating blood over the same period failed to exceed 1.5 mg. per cent, except in 1 case (E. O.), in which, for a short period, the drug was given by mouth. Since 1 pound (453.6 Gm.) of ointment (about 100 Gm. of sulfathiazole) was applied daily to each patient during the first week, it is readily apparent that the amount absorbed was negligible.

This ointment has been widely employed in the University of Chicago Clinics during the past ten months in the treatment of superficial ulcerating areas, abrasions and infected superficial wounds and in the impregnation of gauze packs used in various infected surgical wounds. By and large, the results have been gratifying in more than 150 cases in which the ointment has been employed. The greatest benefit has been observed in cases of infection by staphylococcus, streptococcus or *Bacillus coli*. The least benefit was derived by wounds infected with the common anaerobic organisms.

SUMMARY

A brief résumé of the more important types of treatment of thermal injuries is given.

The importance of plasma in the care of such patients is emphasized, and guides to the administration of this fluid are presented.

Summaries of the case histories of 2 patients and the modes of therapy employed are presented together with studies of fluid balance, blood changes and urinary findings.

Sulfathiazole ointment compounded so that 20 per cent of the drug is contained in an oxycholesterol-petrolatum base is advocated for thermal injuries as well as for other cutaneous injuries.

CHANGES IN THE BODY WATER PARTITION AND EXTRACELLULAR ELECTROLYTES IN SHOCK

CHARLES T. ASHWORTH, M.D.

AND

LOUIS A. KREGEL, M.D.

DALLAS, TEXAS

The present study is an attempt, using the methods available at the present time, to investigate the various changes in the extracellular and intracellular body water, the changes in the electrolytes of the extracellular fluid and the processes of the body in regulating the osmotic pressure of the intracellular and extracellular fluids and an attempt to interpret these changes in the light of presently accepted facts.

Recent studies on the pathogenesis and treatment of shock have dealt particularly with the decrease in plasma volume and the methods of restoring this lost volume. These studies satisfactorily demonstrated the nature and the extent of such plasma volume decrease.¹ The hemoconcentration which occurs in shock, as pointed out by Moon and Kennedy,² is a reflection of this decrease in plasma. Information on the phases of body water other than plasma during shock is almost lacking. Moon³ maintained that in traumatic shock the tissue fluids, presumably interstitial water, are increased owing to widespread escape of plasma from the capillary bed. Dunphy and others,⁴ however, from careful

From the Department of Pathology, Baylor University College of Medicine.

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postmortem studies showed that this increase in tissue fluid occurs only late in the course of experimental burns and traumatic shock and that early the tissue fluids are not apparently increased (gross and microscopic observations). On the other hand, Moon³ said that in hemorrhage the tissues and the body cavities are less moist than usual—apparently indicating a decrease in interstitial water. Blalock⁵ indicated that in early traumatic shock and hemorrhage alike, the tissue fluids are decreased (interstitial water decreased). No recorded studies are available which indicate, in any quantitative degree, the changes in interstitial water, and there has been complete neglect of any consideration of the possible changes of intracellular water in shock or hemorrhage. As a matter of fact, studies of these two phases of body water in any circumstance have been scanty. Gamble and associates⁶ were apparently the first to indicate the possibility of determining relative changes in interstitial and intracellular body water by determining the sodium and potassium balance of the body. Gilman⁷ and Darrow and Yannet,⁸ using this principle, calculated changes in interstitial water and intracellular water after sodium depletion following intraperitoneal injection of dextrose. Gamble and associates reported studies of these body water changes in children under various circumstances. The thiocyanate method of measuring extracellular fluids, introduced by Crandall and Anderson,⁹ constitutes another means of measuring interstitial fluid and, indirectly, intracellular fluid. There is a distinct need for studies of the extracellular and intracellular phases of body water in shock. It is practically impossible satisfactorily to consider changes in body water without at the same time correlating or supplementing with electrolyte studies—particularly studies of sodium and potassium—the chief cations of extracellular and intracellular fluids, respectively. These ions are of significance not only as indicators of body water changes but also as indicators of the body economy in maintaining an equal osmotic pressure inside the cell and in the fluid environment of the cell. Further, in an attempt to understand

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the processes by which the body economy acts in this regard, a study of kidney tubular reabsorption of water and the cations is necessary. No information in this regard is available for the condition of shock and hemorrhage. Scudder, Smith and Drew¹⁰ drew attention to the terminal increase in plasma potassium in shock. Other investigators¹¹ failed to confirm this observation adequately.

METHODS

Dogs were used in all experiments. Samples of blood were obtained from the jugular vein without stasis, and heparin was used as the anticoagulant. Anesthesia was produced by the intravenous injection of soluble pentobarbital, which was seldom repeated after the initial anesthetic dose. Blood pressure was measured by a mercury manometer connected with the carotid artery. Blood volume studies were rather unsatisfactory. The method of Gregersen, Gibson and Stead¹² was used. However, the irregular disappearance of the dye during shock and the almost constant hemolysis despite intense precautions greatly reduced the accuracy of this method. Original volume levels were calculated by this method, however, and subsequent changes were determined by changes in the hematocrit value, the often repeated criticism¹³ being remembered that red blood cells are added to the circulation from the reservoir of the spleen. Extracellular water was calculated as the water available for solution of sodium thiocyanate according to the method of Crandall and Anderson.⁹ Thiocyanate determinations were carried out by the method of Laviètes and others,¹⁴ except that a lumetron photoelectric colorimeter was used to measure the color. Interstitial fluid volume was calculated as the difference between extracellular water and plasma volume. Intracellular water was calculated before shock as 42.5 per cent of body weight, while after shock it was calculated from the total increase or decrease of extracellular water, taking into account the fluid lost during the development of shock, which was measured in each experiment. Hemoconcentration studies, consisting of red blood cell count, hemoglobin estimation, hematocrit evaluation and determination of the specific gravity of whole blood and plasma, were also carried out at intervals during the course of the experiment.

10. Scudder, J.; Smith, M. E., and Drew, C. R.: Plasma Potassium Content of Cardiac Blood at Death, *Am. J. Physiol.* **126**:337, 1939.

11. Bisgard, J. D.; McIntyre, A. R., and Osheroff, W.: Studies of Sodium, Potassium and Chlorides of Blood Serum in Experimental Traumatic Shock, Shock of Induced Hyperpyrexia, High Intestinal Obstruction, and Duodenal Fistulas, *Surgery* **4**:528, 1938. Greenwood, W. F.; Haist, R. E., and Taylor, N. E.: The Plasma Potassium Following Intestinal Obstruction in Dogs, *ibid.* **7**:280, 1940.

12. Gregersen, M. I.; Gibson, J. J., and Stead, E. A.: Plasma Volume Determination with Dyes: Errors in Colorimetry; Use of the Blue Dye, T-1824, *Am. J. Physiol.* **113**:54, 1935.

13. Stead, E. A., Jr., and Ebert, R. V.: Relationship of Plasma Volume and the Cell-Plasma Ratio to the Total Red Cell Volume, *Am. J. Physiol.* **132**:411, 1941.

14. Laviètes, P. H.; Bourdillon, J., and Klinghoffer, K. A.: The Volume of the Extracellular Fluids of the Body, *J. Clin. Investigation* **15**:261, 1936.

Sodium analyses were carried out on blood and urine, the method of Butler and Tuthill being used,¹⁵ while potassium analyses were done by the method of Truszkowski and Zwemer.¹⁶ Urine was obtained through suprapubic catheter in male dogs and through urethral catheter in female dogs. The bladder was washed twice with distilled water before each collection period. Glomerular filtration was calculated by creatinine clearance¹⁷ after the blood creatinine level had been increased by the intravenous injection of creatinine. All analyses were made on heparinized plasma. Using the information available from these blood and urine studies, the tubular reabsorption of water, sodium and potassium was calculated.

Shock was produced by three separate methods: (1) by the intraperitoneal injection of 25 cc. of 25 per cent sodium chloride per kilogram of body weight,¹⁸ (2) by hemorrhage and (3) by trauma to the left hindleg with a blunt hammer. In the dogs shocked by the intraperitoneal injection of fluid, the lost extracellular fluid was calculated by subtracting the volume of fluid injected from the resulting peritoneal fluid. In dogs shocked by hemorrhage, careful measurements were kept of blood removed for sampling as well as that removed to produce shock. In dogs shocked by trauma, the lost fluid was determined by weighing the normal and traumatized legs after bisection according to the method of Blalock.⁵

RESULTS

Table 1 indicates the changes in the various partitions of body water before and after shock in each of the 16 dogs. It will be seen that, with 2 exceptions, the plasma volume was greatly reduced. The reduction was greatest in the dogs shocked by intraperitoneal saline solution, intermediate in traumatic shock and least in hemorrhagic shock. The interstitial water changes, with but few exceptions, were distinct, indicating a striking increase in dogs shocked by saline solution, a decrease in dogs shocked by hemorrhage and an increase in 2 dogs and a decrease in 1 dog shocked by trauma. The intracellular water behaved in an opposite manner, decreasing after saline shock, increasing after hemorrhagic shock and decreasing after traumatic shock. The changes in the size of red blood cells, as shown by mean corpuscular volume, practically invariably corresponded directly, if not proportionally, to the intracellular fluid change.

Table 2 illustrates the changes brought about in the concentration of sodium and potassium in the extracellular fluid and urine as produced

15. Butler, A. M., and Tuthill, E.: An Application of the Uranyl Zinc Acetate Method for Determination of Sodium in Biological Material, *J. Biol. Chem.* **93**:171, 1931.

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17. Rehberg, P. B.: Studies on Kidney Function: I. The Rate of Filtration and Reabsorption in the Human Kidney, *Biochem. J.* **20**:447, 1926.

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TABLE 1.—Changes in the Distribution of Body Water in Shock from Intraperitoneal Injection of Hypertonic Solution of Sodium Chloride, Hemorrhage and Trauma

Experiment	Plasma Volume	Change, * Per Cent	Interstitial Water	Change, Per Cent	Intra-cellular Water	Change, Per Cent	Mean Corpuscular Volume	Change, Per Cent
Saline shock; no hemoconcentration	375 416	+11	1,471 1,756	+20	2,465 2,211	—10	64.5 60.0	— 7
Saline shock.....	403 115	—70	1,897 1,925	+1.5	3,189 3,065	— 3	78.6 75.5	— 4
Saline shock.....	632 193	—71	2,889 3,065	+ 6	5,037 4,861	— 3.5	67.2 57.5	—15
Saline shock.....	326 147	—51	1,401 1,896	+35	2,362 1,867	—21	74.6 67	—10
Saline shock.....	588 253	—57	1,339 1,677	+25	2,700 2,362	—12.5	71.5 64.7	— 9.5
Saline shock.....	1,475 587	—67	2,046 3,333	+39	7,125 5,838	—18	76.1 72.7	— 4.4
Saline shock.....	610 172	—73	1,049 1,541	+48	2,400 2,093	—13	86.1 66.5	—22.5
Shock by hemorrhage; initial hemoglobin, 10.15 Gm.	972 674 †	—32	2,954 2,510	—15	6,460 6,914	+ 6.6	71.8 72.4	+ 0.8
Shock by hemorrhage; initial hemoglobin, 9.5 Gm.	1,620 1,131	—30	3,060 869	—70	5,950 8,372	+29	63.2 72.5	+13
Shock by hemorrhage; initial hemoglobin, 8.55 Gm.	952 388	—59	2,818 2,317	—18	4,930 5,487	+11	63.1 73.2	+13
Shock by hemorrhage; initial hemoglobin, 12.95 Gm.	625 685	+ 9.6	3,757 1,068	—45	3,612 6,271	+70	57.3 60	+ 4.7
Shock by hemorrhage; initial hemoglobin, 14.15 Gm.	425 169	—60	1,365 1,932	+29	3,612 3,523	— 2.6	64.8 66.6	+ 2.8
Shock by hemorrhage; initial hemoglobin, 13.25 Gm.	690 393	—47	2,026 2,073	+ 2.2	2,890 2,845	— 2	60 59	— 1.7
Shock by trauma; traumatized leg weighed +370 Gm.	570 288	—50	3,218 3,627	+11	3,825 3,273	—14.4	72.5 69.8	— 3.7
Shock by trauma; traumatized leg weighed +385 Gm.	530 300	—43.4	1,795 1,600	—11	4,250 4,270	0	72.8 67.1	— 8
Shock by trauma; traumatized leg weighed +600 Gm.	882 473	—46	2,284 2,700	+18	4,250 3,824	—10	62.1 56.6	— 9

* Calculated by changes in hematocrit value.

† Measured by blue dye method.

TABLE 2.—Changes in Sodium and Potassium in Extracellular Fluids and in Urine in Hemorrhage and Shock from Trauma

Experiment	Plasma Sodium, Mg. per 100 Cc.	Change, Per Cent	Plasma Potassium, Mg. per 100 Cc.	Change, Per Cent	Change in Interstitial Water, Per Cent	Urine Sodium, Mg. per Hour	Urine Potassium, Mg. per Hour
Shock by hemorrhage; severe	319 342	+ 7.4	14.0 17.0	+22	—15
Hemorrhage; mild shock	322 336	+ 4.3	18.2 18.4	0	—70
Hemorrhage; mild shock	277 316	+12.0	16.2 14.3	—12	—18	84.4 0.56	47.6 11.9
Shock by hemorrhage; severe	324 307	— 5.2	18.8 27.8	+47	+29	113.0 0.4	34.6 7.2
Shock by hemorrhage; severe	313 326	+ 4.1	19.2 25.6	+33	—45
Shock by hemorrhage; severe	315 329	+ 4.5	15.4 20.4	+32	+ 2.2	3.1 0.1	15.0 0.5
Shock by trauma; severe	334 332	0	23.6 28.2	+20	+11	6.5 19.9	2.8 2.3
Shock by trauma; severe	283 311	+ 6.3	15.6 39.2	+151	—11	54.1 12.0	20.0 0.8
Shock by trauma; severe	337 327	— 8.4	16.2 19.3	+19	+18	9.2 3.76	7.5 0.2

by shock from trauma and hemorrhage. In shock from hemorrhage, the plasma sodium showed, with 1 exception, an increase. Except in 1 instance this change in sodium indirectly corresponded to changes in interstitial water, i. e., when sodium increased, interstitial water decreased and the opposite also was true. The small number of experiments with traumatic shock renders conclusion difficult with regard to changes in plasma sodium in this condition. Table 2 demonstrates also a fairly constant, slight but definite increase in plasma potassium in both hemorrhagic and traumatic shock. In 2 animals in which the increase in potassium did not occur, the shock produced was mild, and the animals were killed.

TABLE 3—*Glomerular Filtration and Tubular Reabsorption* During Hemorrhage and Shock*

Experiment	Glomerular Filtration, Cc. per Hr.	Tubular Reabsorption		
		Water	Sodium	Potassium
Hemorrhage.	1,021	× 28	× 33	× 35
	631	× 53	× 4,000	× 7
Hemorrhage....	2,130	× 47	× 64	× 6
	310	× 62	× 3,000	× 5
Hemorrhage.....	1,375	× 147	× 1,764	× 18
	70	× 70	× 2,000	× 25
Traumatic shock.	1,440	× 120	× 742	× 104
	190	× 30	× 32	× 18
Traumatic shock.	1,200	× 100	× 63	× 9
	125	× 50	× 33	× 25
Traumatic shock..	3,324	× 88	× 46	× 23
	92 5	× 93	× 120	× 92

* Tubular reabsorption figures represent the ratio of glomerular filtrate values per hour to the urine values per hour.

The changes in glomerular filtration and tubular reabsorption in hemorrhagic and traumatic shock are indicated in table 3. It will be seen, as expected, that glomerular filtration falls sharply during shock. In shock from hemorrhage, tubular reabsorption of water is increased definitely, sodium reabsorption increased markedly, the sodium being conserved 2,000 to 4,000 times in its passage through the tubules, while potassium reabsorption tends to be decreased. Strikingly, in traumatic shock, this conservation of water and sodium is absent. Indeed, there tends to occur less reabsorption of these two constituents, while potassium is apparently conserved during traumatic shock.

Table 4 shows a comparison between plasma volume change and actual measured loss of plasma volume. Prominent differences between these values are evident, indicating either an error in the plasma volume

TABLE 4.—*Fate of Plasma Fluid and Interstitial Water in Shock from Intraperitoneal Injection of Hypertonic Solution of Sodium Chloride, Hemorrhage and Trauma*

	Intraperitoneal Injection of Hypertonic Solution Of Sodium Chloride							Hemorrhage					Trauma			
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Experiment																
Measured lost plasma.....	270	400	750	180	255	610	250	315	227	234	167	165	370	385	600	189
Calculated decrease in plasma	+ 41	288	489	179	335	888	438	300†	489	561	+ 60	519	282	230	409	297
volume *								— 15	+ 262	+ 330	— 227	+ 354	— 88	— 153	— 181	+ 109
Fluid lost to or taken from inter-	— 311	— 112	— 251	— 1	+ 80	+ 278	+ 178									
stitial water																

* Measured by changes in hematocrit value.

† Measured by dye method.

calculations or passage of fluid between the interstitial water and the plasma as indicated in the table.

Table 5 is a further representation of these values in hemorrhagic shock as measured by the dye method. The found red blood cell volume and plasma volume levels are compared with the actual measured lost plasma and red blood cells. It will be noted from this table that the decrease in plasma and red blood cell volume is small in view of the fact that definite shock was produced in each instance by bleeding. This fact tends to cast some doubt on the method. However, there was constantly added, according to these studies, a distinct quantity of red blood cells to the circulating blood; further, fluid passed in every instance from the interstitial fluid to the plasma, both of which facts are in accord with present views.

TABLE 5.—*Plasma and Red Blood Cell Volume Changes After Hemorrhage **

Experiment	10	11	12	13	14
Red blood cell volume.....	377 488	695 730	328 439	483 360	317 410
Plasma volume	972 674	1,620 1,455	952 761	625 655	428 540
Measured plasma loss.....	315	227	234	167	165
Total red blood cell change †.....	+278	+ 158	+227	— 25	+207
Fluid passing from interstitial spaces to plasma.....	17	92	43	197	277

* Measured by dye method.

† Measured loss plus increase in blood.

COMMENT

It is necessary to account when possible for the various changes in the partition of body water, extracellular electrolytes and tubular reabsorption of electrolytes, either as direct results of the mechanical, physical and chemical defects of shock itself, or as compensatory efforts of the body processes in regulating the internal environment of the body.

In the dogs shocked by the intraperitoneal injection of hypertonic saline, an extrinsic factor, viz., the introduction of large amounts of sodium and chloride into the extracellular phase, must be taken into account. The passage of sodium ions in this manner must be anticipated since the sodium ion is freely permeable across the peritoneal and capillary membranes and since the osmotic pressure in the peritoneal fluid is vastly greater than that in the extracellular water. Consequently, as a result of this passage of sodium, the osmotic pressure in the extracellular water would be increased. The sodium ion would not be expected to pass into the body cells since the cell membrane is not permeable to sodium. Therefore the body cells would find themselves in a fluid environment with osmotic pressure greater than that in the cells them-

selves, and depending on laws of osmosis and semipermeable membranes, there would be a passage of water from cells to extracellular spaces. Apparently it is this phenomenon which accounts for the increase in interstitial water and the decrease in intracellular water which were found to occur in this type of shock. Apparently the red cells respond in a similar manner to this increased osmotic pressure of their surrounding fluid environment, the plasma, and therefore the red cell fluid decreases; this is shown by decrease in mean corpuscular volume.

In shock from hemorrhage, the changes in interstitial and intracellular water are of an opposite nature, the interstitial water decreasing and the intracellular fluid increasing. There is no reason to anticipate an alteration of the osmotic pressure of the extracellular water after hemorrhage, so that it becomes necessary to assume changes in the cell osmotic pressure in order to account for the change in partition of water. On examining table 1, it may be seen that in all dogs exhibiting marked increase in intracellular water after hemorrhage, the initial hemoglobin level was low. It is thought that in these animals a severe grade of anoxemia was produced by hemorrhage, owing to reduction of the red blood cell mass below the critical level for necessary oxygen transport and in excess of the anoxemia produced in animals with normal control hemoglobin levels. It has been repeatedly stated that anoxemia induces increased osmotic pressure within cells, and this phenomenon, occurring here, would be expected to cause a transit of fluid from the interstitial phase to the intracellular phase. The increase in mean corpuscular volume of the red blood cells in these same animals shocked by hemorrhage would indicate that the red blood cells respond to this situation in a manner similar to the body cells. In these animals, as water passes from extracellular to intracellular phase, unaccompanied by the sodium ion, an increase in the concentration of the sodium ion of extracellular fluids would be expected. Such an increase was found to occur in these experiments.

Why the body should conserve sodium and water after hemorrhage is easy to understand, since the necessity of retention of fluid of normal osmolar concentration is eminent. The means by which this process is brought about by the renal tubules involves considerably more difficult problems. The influence of the adrenal cortical hormone, pituitary hormones and the hypothalamus must be considered, in the light of present knowledge, as the likely regulators, acting together or individually. At least it appears certain that in hemorrhage this regulating or compensating process is available and active.

In traumatic shock, the changes in body water are less regular than after hemorrhage. The evidence is that in traumatic shock interstitial water increases while intracellular water decreases. We are at a loss to account for this difference from hemorrhagic shock. It is possible

that the cell membrane permeability is altered in this type of shock, either under the influence of deficient cortical hormone or as a result of a direct action of some toxic material formed as a result of trauma. Further evidence that some such influence is active is afforded by the studies of tubular reabsorption of water and electrolytes in traumatic shock. The results of this study show a failure of the tubules to conserve sodium or water over the control levels. On the other hand, it may be felt that in traumatic shock there exists an essential difference from hemorrhage in that the fluid lost from the extracellular spaces is not actually lost from the body, nor is sodium lost from the body, and consequently no need for conserving the materials arises.

Although the results of these studies indicate a decrease in interstitial fluid in shock from hemorrhage accompanied by anoxemia and an increase in the interstitial fluid in traumatic shock, it should be reemphasized that these changes take place only partly between plasma and interstitial fluid but largely between the interstitial and the intracellular fluid.

The behavior of potassium in shock has been the source of abundant speculations. Since potassium is the main cellular cation, explanations for the changes in potassium should take into account the physicochemical processes of the cell. In the present studies, it was a notable fact that potassium of the extracellular fluid did not increase until terminally. This terminal increase in potassium in hemorrhagic and traumatic shock may well be the result of a final severe injury of the cell membrane from anoxemia allowing potassium to pass more freely from the cell. It is probably more likely a compensatory effort of extreme type in which an attempt is made to reestablish an equilibrium between the osmotic pressure within the cell and in its internal environment, the extracellular water. As for the tubular reabsorption of potassium there is evidence that the change from before to during shock is in a manner opposite to that of tubular reabsorption of sodium. Further, there is reason to believe that when cellular osmotic pressure is increased, there is decreased tubular reabsorption of potassium and that when cellular osmotic pressure is decreased (or extracellular osmotic pressure increased), there is increased tubular reabsorption of potassium.

SUMMARY

An attempt has been made to investigate the changes in body water—extracellular and intracellular—during experimental shock. In shock from intraperitoneal injection of hypertonic solution of sodium chloride, excess sodium ions in the extracellular fluids raise the osmotic pressure of this phase, causing a transit of fluid from the cell to the interstitial fluid. Thus, an increase in interstitial water and a decrease in intracellular fluid occurs. In hemorrhagic shock, probably owing to increased osmotic pressure within the cell resulting from anoxemia, there is a

passage of water from the extracellular to the intracellular phase. In traumatic shock, for an unexplained reason, the cell water decreases and interstitial water increases.

The changes in the volume of body cells, as shown by the volume of intracellular water, corresponds directly with alterations in the size of red blood cells, i. e., with the mean corpuscular volume.

A parallelism between the concentration of sodium in the extracellular fluid and the volume of extracellular fluid was noted. As interstitial water increased, sodium concentration in the plasma decreased, while the opposite was likewise true.

During shock from trauma or hemorrhage there is striking reduction in glomerular filtration. Tubular reabsorption of water and especially of sodium is increased after hemorrhagic shock, while potassium reabsorption is decreased. In traumatic shock, tubular reabsorption of water and sodium is not increased but may be decreased, while potassium reabsorption tends to be increased. It is thought that these changes in renal tubular function may be related to the function of the adrenal cortex or other water and electrolyte regulators.

In hemorrhagic and traumatic shock a terminal increase in extracellular (plasma) potassium was noted. This is thought to represent an attempt, under the rules of osmosis and semipermeable cell membranes, to equalize intracellular and extracellular osmotic pressure or to represent a severe injury of cell membrane, perhaps due to anoxemia, with increase in cell permeability.

Mr. Fox Miller and Mr. J. W. Ackert assisted in carrying out this study.

PREPARATION FOR OPERATION AND POST- OPERATIVE CARE OF THE PATIENT WITH CANCER

REVIEW OF CONTEMPORARY ADVANCES AND ANALYSIS OF EXPERIENCES
WITH CURRENT CLINICAL PROCEDURES

GREGORY L. ROBILLARD, M.D.

AND

ALFRED L. SHAPIRO, M.D.

BROOKLYN

As the prevalence of cancer increases in accordance with the increasing longevity and advancing age constitution of the general population and as the respective curative spheres of resective and radiation therapies become more sharply defined, the special problems besetting operation on patients with cancer loom larger. Studies in operative care most frequently have been directed toward the general run of operative patients, predominantly persons requiring emergency or elective procedures and constituting for the most part relatively good operative risks. The need for surgical advancement in the field of cancer, in which the prospects hitherto have been held among the least promising, assumes imperative proportions as malignant disease becomes numerically the second most frequent cause of death. There can be no question but that progress will be painstakingly slow, but increased emphasis on the surgical requirements of this clinical group of patients must be forthcoming if medicine is to accept the challenge of the increasing incidence and mortality rate of cancer.

As has been stated, many and perhaps the majority of these patients present in addition to the questions of formidable surgical approaches and technics, associated problems which are probably of greater direct importance in relation to operability and survival. Certainly operative risk and mortality and morbidity rates are more often dependent on these coincident factors than on technical surgical skill. Unlike most candidates for operation, the patient with cancer can in general be considered a chronically ill patient and by the usual standards a relatively poor surgical risk from the outset, requiring major operation of a type that would tax to the utmost the physical resources of a person in good health. However, the constantly increasing number of successful

From the surgical service of Brooklyn Cancer Institute.

operative procedures on patients with cancer bears witness to the desirable results attainable when adequate supportive therapy is afforded and indicates even greater possibilities as the surgical aspects of cancer receive greater emphasis. In this study, therefore, we have sought to focus attention on problems of surgical care pertinent in a greater or a lesser degree to the entire field of surgical procedures for cancer.

In attempting a comprehensive revision of operative care procedures as carried out in our own surgical service and to insure that treatment will be as inclusive as necessary without at the same time sacrificing thoroughness in concentration on details, we have adopted a standard simplified routine suitable for the management of operative patients in a municipal cancer hospital. Operative care outline charts permitting appraisal at a glance of the status of the patient and providing convenient access to all essential data at any time have been found indispensable. These are subjected to periodic modification to incorporate current advances of established merit.

AGE

The majority of patients with cancer are well beyond the physical prime of life and fall into the age group of 50 to 65 years of age. Arteriosclerotic heart disease, pulmonary emphysema, impaired renal function and other degenerative disorders are prevalent at this age. Moreover, fibroblastic proliferation and the associated phases of tissue repair compare unfavorably with the healing powers of the young. However, age should not be generally accepted as a contraindication *per se* to operation, since biometric surveys reveal that the normal life expectancy of persons attaining the age of 60 is from ten to fifteen years. Livingston has pointed out that the potential life salvage in the cancer age group well warrants radical resections entailing a relatively high operative mortality rate. Large series of cases of elderly patients successfully operated on with low associated mortality rates are being reported in increasing and encouraging numbers. Johnson and Lombard stressed, however, the great risk entailed in operations for cancer prolonged over two hours, particularly on patients past 60.

PHYSICAL STATUS

That some degree of degenerative heart disease and generalized arteriosclerosis and attendant deficient circulation exists in the average patient with cancer is a reasonable assumption. Careful appraisal of the cardiovascular status is therefore indicated, since in this group of patients poor circulatory efficiency renders thrombosis, shock and other

postoperative complications major risks. Routine electrocardiography is of particular value to the surgeon in determining operative risk, choice of anesthetic, election of single or multiple stage procedures and similar decisions. Measurement of renal and hepatic function and determination of vital capacity as routine precautions are most apt to afford data of definite importance to the surgeon. Diabetes, anemia, nephritis, prostatism, obesity and perhaps sepsis, which are among the more frequent secondary pathologic entities concomitant to cancer, likewise demand special consideration in evaluating the surgical potentialities of the patient. The patient with any degree of nephritis, whether degenerative or inflammatory, is more susceptible to shock, and a smaller degree of collapse will cause fatal renal failure. In operation, numerous extra-renal factors, including reflex anuria and various types of shock, may result in death from renal failure in the absence of gross primary renal disease. Boyce pointed out that the tendency of surgeons to omit or ignore tests of hepatic function is to overlook the fact that, despite their limited precision, the information these tests afford may prove invaluable, since it is far easier to bolster a damaged liver threatened by anesthesia or anoxemia than a defective kidney or heart.

PREOPERATIVE PREPARATION

The body tissues must be adequately supplied with fluid and electrolytes; metabolism and nutritive reserves of the organism must be restored to as close to normal levels as possible; the respiratory mechanism and the circulatory system must function at their greatest efficiency; the gastrointestinal organs must be in the best possible condition, and the central and autonomic nervous systems should serve under no avoidable handicap. Probably each of the foregoing factors, however, will necessitate some degree of corrective therapy in the average patient with cancer, and several, therefore, merit detailed discussion.

Nutrition.—While in the majority of cases in which operation is done, preoperative care in the main has been considered to devolve on adequate water and salt balance, the crux of supportive therapy in operation for cancer is the establishment of optimal nutrition. It is our usual experience to have patients with cancer enter the hospital after varying degrees of loss of weight. That this postulates ketogenic acidosis, depletion of glycogen and hypoproteinemia to prevail in the average case of cancer in which operation is performed is a matter deserving of far greater general recognition and attention, for each has been conclusively demonstrated to interfere with wound healing and to predispose to operative shock.

In a recent series of 100 unselected consecutive patients admitted to the Brooklyn Cancer Institute on whom operation was contemplated, the following illustrative findings were noted:

Total Blood Proteins:

Normal range: 6.5 to 8 mg.—Below 6.5 mg., 55 per cent

Above 7.5 mg., 10 per cent

Reported range: 3.3 to 9.6 mg.—Repeatedly below 7 mg., 73 per cent

(Only patients with values above 7 mg., in the absence of dehydration are considered by us to have a probably adequate protein reserve.)

In another group of 50 consecutive determinations of carbon dioxide made on newly admitted patients, these data were obtained:

Carbon Dioxide-Combining Power:

Normal range: 53 to 77—Below 45, 17 per cent

Marked tendency to alkalosis

Reported range: 30 to 79—Below 53, 58 per cent

It should be noted that the average value of total proteins discovered among our patients with cancer approximated the "critical level of edema" described by several authors. Ravdin demonstrated that hypoproteinemia is an important inhibiting factor in wound healing, that edema develops at the suture line in enteroanastomosis, resulting in a lack of tissue fusion, and that wound disruption likewise is associated with this deficiency of protein. Hartzell, Winfield and Irvin noted that serum protein and ascorbic acid values in cases of wound disruption are decidedly lower than normal. The frequency of wound disruption after operations for cancer is notable. In several cases at the Brooklyn Cancer Institute, the total protein level ranged from 4.9 to 5.2 mg., thus apparently confirming Ravdin's hypothesis. Maintenance of liver function and its protection against anesthetic and toxic injury, heretofore accepted as primarily dependent on adequate administration of carbohydrates, was likewise shown by Ravdin to be enhanced by a high protein and carbohydrate and low fat diet. It was his concept, in accordance with that of several other workers, that a lowered serum protein level is generally associated with damage to the liver and injury to the hepatic plasma protein regenerative mechanism rather than with simple protein malnutrition. Likewise important is the role played by hypoproteinemia in the causation of both peripheral and visceral edema, particularly pulmonary, as well as by the associated inhibition of gastrointestinal activity, which may, especially after enterostomy, favor the progress of adynamic ileus and increased predisposition to shock.

We find, as have others, that the most desirable practice is the administration of a 3,000 calory diet, consisting roughly of 70 per cent carbohydrate, 25 per cent protein and less than 5 per cent fat, resulting

in a nonketonic acid residue to favor healing. Tissue regeneration and cellular proliferation can hardly be anticipated without proper nutrition, and since it must be recognized that absorption and assimilation of abundantly provided nutrients, vitamins and minerals may be defective in cachectic patients with cancer, whenever parenteral administration is of demonstrable supplementary value, it should be employed. In instances of parapyloric obstruction, sterile, partly digested protein-carbohydrate or multiple aminoacid-carbohydrate nonresidue preparations, such as several commercial vitamin-reinforced products now marketed, are best administered by orojejunal tube feeding. Ice cream mix provides an admirably proportioned base to which vitamins may be added. Repeated plasma infusions or, if plasma is unavailable, blood transfusions to raise the serum proteins to normal values are frequently required. It has been shown that 500 cc. of plasma daily is sufficient to maintain nitrogen balance.

The Miller-Abbott tube or a modification of it may be utilized in cases of obstructive lesions of the gastrointestinal tract for maintaining nutrition. In treating lesions of the pyloric level, drainage is carried out above, and feeding below, the site of obstruction. For lesions below the absorptive levels of the small intestine drainage is maintained at the point of block, and feeding, above this point. Parenteral administration of protein (e. g., casein) hydrolysates and amino acids appears feasible and promising. Falconer found that a rise in the blood urea content indicates increased endogenous protein metabolism in cases of intestinal obstruction and thus serves as an index to the condition of the patient.

Holman, Whipple, Hartzell, Snell and others recently drew attention to the important surgical roles of vitamin and protein factors in post-operative recovery. Snell emphasized that dangerous avitaminosis may be precipitated in many persons because of long illness and limited diet when the insults of anesthesia, surgical procedures and further reductions in food intake in the postoperative period are added. Thus Yavorsky found on analysis that tissues and organs of all patients over the age of 46 years were lacking adequate amounts of vitamin C. Hartzell demonstrated that patients with malignant growths of the gastrointestinal tract have low vitamin C values. The metaplasia of epithelial structures, their poor healing response and the impaired resistance to infection of the skin and the respiratory and gastrointestinal mucosas attendant on avitaminosis must receive full consideration from the surgeon. Crile expressed the opinion that the parotitis after operation on the colon is related directly to insufficiency of vitamin A. In addition to being required for proper maintenance of heart and neuron axis function and gastrointestinal tone, vitamin B components appear essential for blood regeneration. Furthermore, as vitamin B₁ is a coenzyme in the metab-

olism of dextrose, administration of large amounts of carbohydrate parenterally has been reported to result in acute shortage of this vitamin, requiring, therefore, an adequate vitamin B₁ complement. Mackie cited several cases of malignant disease with deficiency of vitamin K in the absence of jaundice, a subject which will be more fully discussed later. Vitamin P, or citrin—the recently announced purpura-preventive factor—appears to be related to the integrity of capillary membrane action and thus plays its role in the healing process.

The safe surgical assumption, since patients with cancer as a group are both middle aged and suffering from inanition, is that cancer presupposes surgical avitaminosis. Modern concepts of adequate pre-operative preparation then require that an adequate reserve of vitamins be built up routinely before operation is undertaken on any patient with cancer. Spies stated pointedly that malnutrition tends to be associated with mixed rather than single deficiency diseases and indicates a simultaneous lack of calories, protein, calcium, phosphorus, iron and at least several vitamins. Butt and Leary repeated that massive doses are generally required to counterbalance serious depletions of the vitamins.

Fluid and Electrolyte Balance.—In patients with cancer the problem of restoring fluid and electrolyte balance frequently assumes more complex dimensions than in the everyday operative patient in whom routine administration of several liters of parenteral fluids has often sufficed despite a lack of consideration for individual needs. Fluid and electrolyte imbalance should be assumed to exist in patients with cancer until carefully ruled out, particularly in face of the fact that gastrointestinal lesions account for the majority of cases in which operation is accepted as the foremost means of therapy. It is in dealing with patients in this category that a history of protracted vomiting, diarrhea, starvation or obstruction with attendant dehydration and loss of electrolytes is so frequently elicited, and it requires carefully planned measures to combat them effectively.

In our service the whole blood chlorides were found among 100 patients on admission to the hospital to range from 396 to 742 mg. (The normal whole blood chloride range is from 430 to 520 mg.) Among our patients on admission to the hospital 45 per cent had whole blood chlorides below 450, and 60 per cent, below 475 mg. Only 18 per cent had whole blood chlorides above 500 and probably had a dependably adequate chloride and sodium reserve. Hypochlorinemia, then, is a common finding in candidates for operation for cancer.

Clinical dehydration exists when approximately a 6 per cent loss of body fluids occurs. In instances of losses of body water exceeding 10 per cent of the total, death may ensue. Moreover, dehydration is

generally accompanied by a deficiency in body electrolytes with resultant acidosis or alkalosis, since the major avenues for fluid depletion contribute equally toward coincident diminution of salt reserves.

For the proper maintenance of the balance between fluid intake and output, the ordinary salt requirement is only about 5 Gm. daily. Fluid imbalance supervenes if there is a disturbance of intake, output or retention mechanisms of either water or salt or both. If salt is in excess, the kidneys conserve water; this results ultimately in tissue edema. If salt is lost, however, e. g., by vomiting, the kidneys excrete water with consequent dehydration and hemoconcentration. Newburgh demonstrated that the average nitrogenous waste material excreted by the kidneys amounts to some 35 Gm. daily. A minimum of 500 cc. of urine, at a specific gravity exceeding 1.030 is required to carry out this process of elimination. At a specific gravity of 1.010, that characteristic of filtrative, but for all practical purposes, nonreabsorptive kidney action, excretion of 1,500 cc. of urine daily satisfactorily takes care of nitrogenous catabolites.

The rule of Maddock and Collier that urinary output of operative patients should be maintained, if possible, at 1,500 cc. in twenty-four hours may therefore be taken to indicate adequate elimination at practically all ranges of kidney function. As a corollary, it has been pointed out that the patient under these circumstances is but exceptionally a subject for anxiety with regard to sodium chloride and water and acid-base balance. The healthy kidney is capable of excreting 35 to 40 Gm. of excessively administered salt daily. Beyond that amount, retention of salt and water occurs. The normal acid-base balance of the blood has for its important regulatory mechanisms the hemic carbonic acid and hemoglobin blood buffer and the chloride-shifting systems, the pulmonary exhalation of carbon dioxide and the excretion of renal ammonia and sodium phosphate. Within relatively narrow limits, loss of either the anions or the cations of the essential body electrolytes may be compensated for, e. g., by the renal shift to more alkaline phosphate excretion in the chloride loss of emesis, but protracted electrolyte loss leads to serious acidosis or alkalosis, depending on the nature of the predominant ions sacrificed; this is indicated by marked alterations in the carbon dioxide-combining power of the blood. An essential item in operative care charts is therefore a carefully itemized account of fluid and salt debits and credits.

Persistent emesis may often be an accompaniment of gastric or colonic disease. If the hydrochloric acid of a relatively normal gastric secretion is the major depletion, alkalosis supervenes. If the predominantly basic enteric secretions are repeatedly drained away in the

vomiting associated with obstruction low in the intestines, the more frequent syndrome of relative acidosis is encountered. Not infrequently, in the interim between stages of complicated surgical procedures profusely draining gastric, ileal or biliary fistulas may detract materially from the alkaline reserves. The use of Levine and Miller-Abbott tubes and Wangensteen suction drainage apparatus must frequently be resorted to, and all too commonly the added drain on body fluid and salt is overlooked. Since liquids and salt are both ingested and secreted in the upper part of the gastrointestinal tract but are probably dependent in the main for absorption and reabsorption on the normal function of the lower part of the ileum and the colon, great care must be taken lest combined oral feeding and suction drainage serve only to handicap the patient further by drawing into and away from the intestinal tract salt and water containing secretions well above the water-salt absorptive area, thus leading to even greater dehydration and acidosis. Since the salt loss by bowel normally is merely 0.5 Gm. and the water excreted in feces is less than 100 cc. daily, prolonged diarrhea also will signify uncompensated rectal diversion of considerable amounts of both fluid and electrolytes and impaired colonic absorptive activity. The normal skin excretion may be augmented to a marked degree by elevation of temperatures, increase of perspiration or profuse serous or purulent drainage.

In treating the majority of patients with acute or elective indications for surgical intervention, one is dealing with a local lesion and comparatively little general disturbance, requiring primarily the suitable adjustment of only salt and water. In the chronically ill, such as patients with cancer, inherent disturbances of normal sodium chloride and water retention mechanisms may require that these substances be given under strict scrutiny. The hypoproteinemia that has been shown to be characteristic presages increased susceptibility to edema. Casten and Bodenheimer described the plasma protein value of 5.5 ± 3 mg., not as a critical, but as a relative, edema level, depending on the intracapillary hemostatic pressure, the permeability of capillary walls and the salt-water partition as other major variables involved. Either impaired hepatic synthesis or malnutrition makes for a deficiency in the available labile liver protein. In marked instances of total base deficiency, another finding not rare among patients with cancer, Scudder, Peters and Gamble agreed that, owing to a mechanism as yet uncertain, maldistribution of sodium, chlorine and water may lead to untractable edema which is not influenced, unless the patient improves clinically, by giving the calculated requirements of salt and fluid. Administering sufficient plasma and sodium lactate to correct hypoproteinemia and make up the deficit in alkali may in favorable instances be followed by more normal regulation of salt and water.

Fluids Administered.—(a) Dextrose-Saline Solutions: Dextrose-saline solutions, generally as equal mixtures of 10 per cent dextrose and either 2 per cent or physiologic solution of sodium chloride are frequently ordered as a routine postoperative measure without proper respect for their actual indications. However, an important contraindication to the prolonged use of dextrose-saline mixtures is the fact that in the absence of any deficiency of salt, an excess of sodium chloride may inadvertently be given. Four liters of a 5 per cent dextrose-saline solution contains about 20 Gm. of salt, four times the necessary ration of 5 Gm. daily. In the chronically ill patient with cancer whose kidneys are not functioning at maximum efficiency or with concomitant hypoproteinemia, edema is prone to ensue, particularly with the prolonged periods of parenteral administration of fluids usually required.

(b) Saline Solutions: Solutions of sodium chloride are required primarily to make up for proved deficits of sodium chloride. The normal sodium chloride requirement of 5 Gm. daily can be provided for by the liter of physiologic solution of sodium chloride given once a day. Since isotonic solutions are best tolerated and since fluid losses occur in isotonic quantities and, finally, since the value of hypertonic or hypotonic solutions is at best controversial, it is probably best to utilize isotonic preparations only, unless definite indications to the contrary obtain.

It is always important to maintain the blood chloride level above 450 mg., preferably at about 560 mg. Although several supposedly more exact methods of estimating the needed amount of saline solution have been proposed, the second clinical rule of Maddock and Collier has provided for us a yardstick that is easy to use, namely, for every increase of 100 mg. of blood chlorides desired, give 0.5 mg. of sodium chloride per kilogram of body weight. As a matter of practice, in a person of average weight, an increase of 100 mg. requires about 4 liters of physiologic solution of sodium chloride. Two to five days, depending on the quantities required, should be taken to make up the deficit, in accordance with the findings of Fantus that sick patients do not tolerate well the rapid intake of large amounts of fluid. Gamble demonstrated that solution of sodium chloride serves to make the adjustments necessary in the usually encountered degree of acidosis or alkalosis, since the healthy kidney will selectively excrete the sodium or the chloride ion depending on which is in excess. Several reports seem to indicate that Ringer's solution is less conducive to retention in the sick operative patient and is therefore to be preferred in difficult cases. Peters stated that small amounts of 2 or 5 per cent hypertonic solution of sodium chloride may prove to be of value toward raising the osmotic pressure of the plasma and withdrawing fluid from the tissues when sodium chloride appears to be bound to the interstitial fluid in the presence of

both hypochloremia and hypoproteinemia, although 25 per cent solution of dextrose in water is recommended if the blood chlorides are normal.

(c) *Dextrose Solutions*: Solutions of dextrose are preferably given in the isotonic 5 per cent strength. When additional carbohydrate for energy or for combating ketosis or liver damage is required, dextrose may be given in a 10 per cent solution. However, the urinary output must then be watched to insure that the hypertonic solution of dextrose does not result in transitory diuresis and consequent further dehydration. Given parenterally, 250 to 500 cc. per hour of 5 to 10 per cent solution of dextrose is oxidized as readily as if given by mouth and does not as a rule result in glycosuria. The water serving as the vehicle is then liberated for the normal fluid requirements of the body. It must be borne in mind, on the other hand, that prescribing dextrose solutions alone aggravates electrolyte deficiency coexisting with dehydration. Moreover, recent investigations showed that prolonged administration of dextrose solutions exclusively may precipitate acute avitaminosis B, since the vitamin B complex functions as a coenzyme in the intermediary stages of carbohydrate metabolism, unless vitamin B supplements are given. In the presence of clinical dehydration, when fluid by mouth cannot be ingested, approximately 3,500 cc. of a 5 per cent dextrose solution, to make up for the 6 per cent body fluid loss in a patient of average weight, is added gradually over several days to the 3,500 cc. daily metabolic requirement.

(d) *Hartmann's Solution*: Hartmann's solution as a 6 molar concentration of sodium lactate in Ringer's solution appears to be preferable to the likewise isotonic 5 per cent solution of sodium bicarbonate occasionally indicated as an emergency measure to combat extremes of acidosis or, by its buffering action, alkalosis.

The admonition to force fluids is often erroneously held to apply to postoperative care. In the middle-aged group, among whom the incidence of cancer is greatest, it must be realized that the indiscriminate addition of fluids parenterally carries the real threat of overtaxing the circulation and precipitating pulmonary edema or congestive heart failure or, exceptionally, acute cardiac dilation. Fluid given at a rate in excess of 15 cc. per minute has been demonstrated to accelerate the heart rate in young persons, and with diminished cardiac reserve it may cause pain or produce pulmonary edema. Fishberg stated that there is no appreciable increase in cardiac work below this rate, however, and indicated that it may be safely adopted as an upper limit in patients with cardiac disease or hypertension. Coller and Maddock pointed out that 250 to 500 cc. per hour is a safe rate which will not overload the normal heart. To forestall the onset of serious circulatory insufficiency, the patient should be repeatedly checked for a reactive rise in the pulse

rate and the blood pressure. The lung bases, the lower eyelids and the dependent portions of the body also should be examined several times daily for evidence of anasarca. Increased filling or distention of the peripheral veins, notably the jugular and the cubital, associated with the sudden appearance of cough or progressive dyspnea may indicate the onset of congestive heart failure. Surgical edema, then, because of the relative renal insufficiency of later life as well as the reasons previously mentioned, is somewhat more apt to occur in patients with cancer, who as a rule require prolonged parenteral administration of fluids. While subcutaneous edema may impair wound healing, pulmonary edema so induced may cause death.

Murphy, Correll and Grill recently demonstrated that isotonic solution of sodium chloride after four hours will still have produced an increase in plasma volume of one-fifth the volume of fluid administered regardless of the rate and that the addition of 8 grains (0.52 Gm.) of theophylline with ethylene diamine greatly diminishes this effect. Alternating this with a 5 per cent solution of dextrose likewise decreases both this tendency and that to increased venous pressure and to edema. Volumes exceeding 50 cc. of 50 per cent solution of dextrose, despite the addition of 8 grains of theophylline with ethylene diamine, failed, unlike the smaller amount, to improve pulmonary edema, cardiac dyspnea, decreased venous pressure or increased urinary output but on the contrary aggravated the condition of the patient, often precipitating cardiac failure. Mercurial diuretics by intramuscular injection in doses of 2 cc. or by suppository also may be used in the relief of edema. As an emergency procedure, phlebotomy and withdrawal of up to 500 cc. of blood may be indicated. Hypertonic plasma in 100 cc. quantities of a fourfold concentrate after the withdrawal of 500 cc. of blood appears to be a recently proposed effective remedy.

For routine purposes of maintaining fluid balance parenterally, we have adopted the following procedure in our service: If no loss of body fluid has occurred, 1,000 cc. of a 5 per cent solution of dextrose in distilled water is given by continuous intravenous drip over a period of two hours or of three hours in cases of suspected cardiac disease, in early morning and late afternoon. At noon, 1,000 cc. of physiologic solution of sodium chloride is given by hypodermoclysis into the thigh or directly into the vastus muscles, since pectoral infusions may hinder respiration. If pain is complained of, 25 cc. of 1 per cent procaine hydrochloride added to the solution of sodium chloride may give considerable relief. In the older patient, the subcutaneous route has several advantages, i. e., the relatively slow absorption is less apt to tax the circulation and poor absorption may be taken to signify impending edema or impaired circulatory function. Charted losses of body fluid are

replaced volume for volume by isotonic solution of sodium chloride or Ringer's solution. Unless urinary excretion is maintained at 1,000 to 1,500 cc. per twenty-four hours, blood and urinary chlorides, plasma protein and Van Slyke values are checked repeatedly for guidance in further therapy.

Prevention and Treatment of Shock.—Although considerable disagreement exists as to the exact pathologic physiology of shock, sufficient conclusive evidence concerning the contributory roles of inadequate blood volume, improper blood constituents and abnormal vascular tone to render their avoidance of maximum importance in the prevention of shock has been propounded. Moon depicted this sequence of events: Various noxious agents produce capillary atony; increased capillary permeability ensues, resulting in hemoconcentration and reduction in circulating blood volume, leading to tissue anoxemia. This leads to further capillary atony, establishing a vicious circle. The concomitant peripheral vasoconstriction and splanchnic vasodilation are still of controversial import. The toxic hyperpotassemia, emphasized by Scudder as indicative of profound cell injury, in Blalock's opinion plays a secondary part. Predisposing to an inadequate blood volume in the patient with cancer are the characteristically associated dehydration, chronic or acute blood loss, deficient plasma proteins and increased capillary permeability as a consequence of inanition, toxemia or the relative anoxemia of an impaired circulatory system and acapnia. It is wisest, therefore, to look on the average patient with cancer as specifically susceptible to surgical shock and to undertake the necessary combative measures as a routine precaution. Proper attention to nutritive requirements and plasma infusions to raise the serum proteins and specific gravity is doubly important in this regard. It may be roughly predicted that a liter of plasma will produce a rise of 0.2 mg. in the plasma protein level. The latter is best maintained above the value of 6.4. If hepatic protein regenerative synthesis is impaired, any gain may be lost after twenty-four hours, and frequent maintenance transfusions of plasma concentrates may prove essential. Needless to say, correction of acid-base imbalance and measures to minimize toxemia will tend to render capillary permeability more nearly normal. Except through the possible medium of extract of adrenal cortex, it has not been possible until the present specifically and directly to decrease capillary permeability. However, Hill quoted Krogh to the effect that concentrated plasma appears to improve vascular tone and the permeability of capillary walls. Measurement of the hematocrit value, the plasma protein and the plasma specific gravity are particularly invaluable procedures in the prophylaxis and early therapy of shock in the patient with cancer, in view of the latter's predisposition to this complication,

and should be routinely adopted in the management of this type of case. Falling hematocrit values demonstrate the necessity of blood transfusions and are suggestive of hemorrhage, while rising values indicate the hemoconcentration attendant on dehydration and early or impending shock and signify the necessity for fluid or plasma, respectively; if proteins drop without parallel similar change in hematocrit readings, protein plasma supplements are indicated, while if both hematocrit and plasma readings are low, whole blood may be given. Specific gravity determinations serve as a rapid check on the protein level of the blood and are easily performed at the bedside.

The standing orders in our service require that the patient shall never be left unattended during the first two hours and is to be kept under constant observation for shock and hemorrhage. Citrated blood (500 cc. to 1 liter) of compatible type is kept immediately available during and after the operation. Blood pressures are read every half hour for the first two hours, then at hourly intervals for four hours and thereafter two to four times daily for one week, with the mental reservation held to the fore that a marked fall in the blood pressure indicates relatively late advancing shock. Kekwick stipulated that 3 liters of blood or plasma may be required to elevate the blood pressure above 100 mm. in the patient in shock.

It should be pointed out that the common practice of confusing the problems of fluid-electrolyte balance and shock may prove to the considerable disadvantage of the patient with cancer. Peters and Blalock, among others, demonstrated that in patients in shock the administration of large amounts of solutions of sodium chloride or dextrose may serve temporarily to bolster the circulating blood volume, but thereafter the water given leaks rapidly into the tissue spaces, thereby washing still more proteins into the blood, or is rapidly eliminated by the kidneys, resulting in a more seriously handicapped patient than before, since the plasma volume and the osmotic pressure have been even further reduced and the interstitial fluid and the sodium chloride content increased. To combat shock by forestalling the increased fluid-electrolyte loss consequent to a prolonged surgical procedure calls for the essentially prophylactic administration by continuous intravenous drip of no more than 1 liter of solution of sodium chloride during the initial phase of the operation. Since the blood volume in shock or hemorrhage requires rapid restoration, this may be given at the rate of 20 to 40 cc. per minute until the pulse rate and the blood pressure improve. Additional amounts are harmful if this proves to be of no avail, and prompt substitution of continuous blood infusion at a rate determined by the depth of the shock reaction is called for. If no blood is immediately available, a 6 per cent acacia-Ringer's solution may serve, albeit undesirably, as a temporary expedient.

Recently, Scudder, Perla and several other investigators advocated the use of extract of adrenal cortex in the prevention and treatment of shock. In our hands, the initial results in a few cases have been inconclusive, but we are at present engaged in further study. It is held that this procedure enhances salt and water metabolism and tends to neutralize the hyperpotassemia reported to be present in shock. Several late studies seemed to indicate a marked superiority of extract of adrenal cortex, preferably in large doses, over desoxycorticosterone acetate, the synthetic preparation. A 5 per cent solution of sodium chloride, 300 to 500 cc., given intravenously appears to be of some value in treating prolonged shock to augment the action of a liter or more of blood or plasma in maintaining the blood pressure, if this begins to fall again. The specific value of solution of sodium chloride in the treatment of shock, according to Scudder, is that it may dilute the inspissated blood in hemoconcentration, increase the velocity of circulation, decrease the generalized vasoconstriction and increase the elimination of potassium through the kidneys.

We believe that routine postoperative assumption of the Trendelenburg position, by increasing the carotid and thus the cerebral circulation, as shown by Mann, is a worth while adjunct in both prevention and treatment of shock. Further, it is of value in precluding the aspiration of nasopharyngeal and bronchial secretions and vomitus. Recently, from the Mayo clinic there emanated the novel and ingenious suggestion that patients be kept in Fowler's position for three days before operation and thus accumulate a 1,500 cc. reserve of tissue fluid in the lower extremities. During operative procedures, assumption of the Trendelenburg position taps this reservoir, which, as an autotransfusion mechanism, prevents shock. Preventing the chilling of the patient by means of warm light blankets and hot water bottles is a frequently overlooked step directed against the development of shock. However, this must be done within limits not conducive to increased perspiration or marked peripheral vasodilation, for either will augment shock. Moreover, Blalock demonstrated that in experimental shock, once developed, the application of cold leads to longer survival than the application of heat.

Stimulative medication has proved in our hands to be relatively valueless in the therapy of shock, bearing out the thesis that restoration of circulating blood volume is the physiologically effective mode of therapy. In agreement with Fishberg and Tainter, we may state the sympathomimetic amines, notably, epinephrine and ephedrine (the latter given intravenously in emergencies as vasoconstrictors), seem serviceable to some extent but solely as temporary expedients for elevating the blood pressure. According to Best, pitressin, if administered prior to serum, results in less capillary leakage and a more sustained rise in blood pressure. However, camphor, strychnine and similar drugs appear to be

of no real worth, and digitalis is definitely contraindicated because of a tendency to increase peripheral vasodilation. Best and Solandt and Harkins questioned whether the physician may reasonably anticipate permanent recovery when blood pressure has fallen to the clinically low levels at which vasoconstrictors are used. Dunphy likewise stressed the irreversibility of advanced shock. The analeptic action of coramine (a 25 per cent solution of pyridine betacarboxylic acid diethylamide), metrazol and picrotoxin in proper dosage in neutralizing the depressant action of prolonged anesthesia or of sedative and analgesic barbiturate preparations tending to deepen shock is acknowledged, but their place in the specific treatment of shock is difficult to evaluate. The administration of high concentrations of oxygen or of carboxygen (a mixture of carbon dioxide and oxygen), if acapnia or shallow breathing is present, seems, however, to provide material assistance to the patient with hemoconcentration, peripheral circulatory collapse and attendant tissue anoxia and should not be omitted.

Harkins was inclined to state that older patients may possess diminished compensatory adrenal potentialities and that their less pliable vasculature is less dependable for the maintenance of an adequate blood pressure in circulatory emergencies and are thereby more susceptible to shock. Intravenous giving of fluids as preventives and prompt administration of blood and plasma are the sine qua non of modern shock therapy, with oxygen and extract of adrenal cortex as promising adjuvants.

Preventing Gastrointestinal Complications.—In disturbances of the gastrointestinal tract amenable to amelioration before operation, steps toward this end should be taken, since restoration to relatively normal function lessens the likelihood of postoperative difficulties. In cases of gastric carcinoma, copious lavage with isotonic solution of sodium chloride is carried out the night before and repeated in the morning two hours before operation until returns are clear. One tenth per cent hydrochloric acid in physiologic solution of sodium chloride is used in the event of achlorhydria. When indicated, a Levine tube is left in situ for passage through an anastomotic stoma, as prophylaxis against distention and for initial fluid intake.

In cases of diseases of the colon and the rectum, irrigations of the colon with isotonic solution of sodium chloride are also carried out the night before and repeated on the morning of operation until returns are clean. In cases of obstructive growths of the sigmoid and the rectum an attempt is made to insert an indwelling rectal tube beyond the obstruction via a proctoscope for several days of preoperative high colonic saline irrigations. In some cases saline purges for several days before operation may be ordered, but purgation to the point of robbing the body of needed salt and fluid is avoided. By keeping infected gastric and

colonic content at a minimum, the obvious dangers of peritoneal spill when the lumen is entered are lessened. Moreover, restoration of normal peristalsis seems to have a worth while effect on the smooth muscle tonus of the digestive system. The method of relieving intestinal obstructions by means of suction drainage via a Miller-Abbott tube and the necessary precautions against coincident fluid-electrolyte waste have already been discussed. It seems that in cases of intestinal obstruction supervening on enteric neoplasms the value of conservative therapy has been safely established. It is necessary, however, to make certain of the vascular integrity of the bowel segments involved before placing primary dependence on a Levine or a Miller-Abbott tube.

Our routine in intestinal operations calls for limited administration of fluids by mouth after twenty-four to twenty-eight hours, preferably deferred until after flatus is passed freely. Sips only are allowed at first, thereafter 1 ounce (29.6 cc.) per hour may be given until 8 ounces (236.6 cc.) have been retained, and then increased amounts are allowed. As soon as permissible, the patient is allowed a soft fluid-like low residue diet high in vitamins and hematinic components. Foster, substantiated by Peters, showed that the gastrointestinal systems can be put at absolute rest postoperatively if nothing whatever is given by mouth, despite the continuance of gastroenteric secretion for a brief while. For the first day, gastric lavage with solution of sodium chloride may be necessary to control vomiting of accumulated gastric secretions and regurgitated bile, but when a prolonged healing period of the gastrointestinal tract is imperative, for the ensuing forty-eight to seventy-two hours all fluid should be taken parenterally.

Postoperative distention and gastric dilation must be watched for carefully during the first three or four days. Persistent vomiting and distention are as a rule readily controlled by simple gastric lavage with isotonic saline solution. If continuous gastric suction drainage is instituted, it cannot be too often emphasized that chloride and carbon dioxide determinations are required daily in addition to regulated subcutaneous or intravenous volume for volume restoration of the fluid and electrolytes drawn off. It is recommended that the tubes be clamped every two hours with a view to determining how well the patient can tolerate the early discontinuance of suction drainage. Prostigmine methylsulfate in doses of 1 ampule given immediately preoperatively and thereafter every two or three hours for four to six doses has been used to prevent both postoperative intestinal atony and distention and bladder atony and retention of urine. Another procedure recently advocated for the relief of distention is the inhalation of 95 per cent oxygen for a twelve hour period. The insertion of a rectal tube serves to relieve the gas pains of lower intestinal origin. Enemas, however, are best deferred for four to five days as a rule. Pack substantiated the findings of Puestow that morphine,

prostigmine methylsulfate and physostigmine salicylate stimulate the small bowel but inhibit the action of the large bowel, while pitressin has the reverse effect on intestinal tonus, and pointed out that the indications for their individual use therefore vary, depending on whether relief of upper or lower gut distention is sought. If adynamic ileus supervenes, it may be necessary to resort to spinal anesthesia should other measures fail. Should pitressin induce a late drop in the blood pressure, ephedrine may be needed to counteract this.

Preoperative Preparation of Circulatory and Blood Systems.—(a) Heart and Blood Vessels: As has been pointed out, operative risk is greater in the presence of the types of organic heart disease commonly found in patients of the cancer age, but these conditions are not of themselves an absolute contraindication, and routine electrocardiographic reading in this age group is of obvious advantage. However, if the patient states that he is free of dyspnea or chest pain on ordinary exertion, it is reasonably certain that the functional capacity of the heart will not be overtaxed by the operation except in the relatively rare situations in which sudden death is precipitated by syphilitic aortitis, aortic stenosis, severe heart block or concurrent coronary thrombosis. Preoperative sedation with barbiturate for several days (narcotizing doses being avoided) to allay apprehension is strongly recommended by Blumgart as well as several preliminary test doses of morphine sulfate to forestall a dangerous synergistic effect of suddenly superimposed barbiturate, morphine and anesthetic. Cardiac decompensation at rest necessarily contraindicates all but extremely urgent surgical procedures of an emergency nature. Although digitalization as a routine supportive measure is to be condemned, since it adds to toxicity when it is of no clinical avail, to correct cardiac failure or combat the presence of auricular fibrillation (the latter in itself is not a contraindication to operation) it should be carried out. When severe hypostatic congestion is found and rapidity in therapy is demanded, the use of strophanthin and mercurial diuretics is indicated. Theophylline with ethylene diamine or one of the related xanthines is indicated in cases of agina pectoris and coronary sclerosis as a useful preoperative adjunct for coronary vasodilation.

Levine reiterated that the well compensated patient with organic heart disease will, in general, stand major operations satisfactorily. It may be briefly mentioned here that although procaine hydrochloride as a local anesthetic is productive of the fewest electrocardiographic irregularities and chloroform, of the most, either is apparently well tolerated if a local anesthetic will not suffice; this is true also of cyclopropane. However, it is a fact to be borne in mind that anesthetic agents, epinephrine or anoxemia may sensitize the arteriosclerotic heart and induce ventricular fibrillation or tachycardia (a complication which should be prepared against by the surgical and anesthetic staffs).

Consideration should be given in all cases of limited cardiac reserve to the prophylactic use of oxygen therapy. During the stage of anesthesia, high oxygen concentrations are essential to prevent the deleterious cardiovascular and hepatic effects of anoxia. Lundy reported that the major contraindication to inducing anesthesia with intravenous sodium pentobarbital is a cardiac lesion associated to any extent with congestive symptoms. Among drugs to be given with extreme care to patients with heart disease Blumgart cited pitressin (used for distention) and epinephrine since their vasoconstrictor action may precipitate angina pectoris and subsequent collapse. Atropine used indiscriminately may lead to runaway tachycardia.

Since operation among patients with cancer and the middle aged and elderly is on the increase, studies to develop optimum operative technics applicable to this class of patients, with special consideration afforded to the problem of avoiding cardiovascular deaths, must be carried out to formulate standards for the best attainable end results.

(b) Blood: The fact that most patients with cancer have a degree of anemia sufficient to retard wound healing, predispose to shock or, as was recently demonstrated, facilitate the onset of edema when a solution of sodium chloride is given parenterally, seldom receives the consideration it deserves.

Hemoglobin and red blood cell determinations carried out on 100 consecutive patients admitted to the surgical services of the Brooklyn Cancer Institute revealed the following figures:

Hemoglobin Percentage:

Normal range: 80 to 105 per cent

Reported range: 42 to 91 per cent

Below 50 per cent, 10 per cent of the cases

Below 65 per cent, 65 per cent of the cases

Above 75 per cent, 24 per cent of the cases

As a check on the accuracy of these findings, it may be noted that 90 per cent of hospital workers periodically tested had hemoglobin values above 85 per cent.

Despite the fact that not all our patients seeking hospitalization for various forms of cancer have cancer in an even moderately advanced stage, some degree of anemia is found to be present in almost all. In this connection, recent experimental work emphasizing a correlation between cancer and hemolysis, disturbances of bilirubin and hemoglobin metabolism and anemia is of added interest. Contributory as well to the development of anemia are: the gross or occult hemorrhage of gastrointestinal or genitourinary lesions; a deficiency in the intrinsic hemopoietic factor of Castle (in the presence of achlorhydria); anorexia and consequent iron and other mineral malnutrition frequently seen in all types of

moderately advanced cancer, and decreased intake of other extrinsic hemopoietic ingredients.

Another phase of the problem of anemia in the patient with cancer that requires attention was brought out by Wills and Elliott, who stressed the often overlooked fact that anemia may develop postoperatively in the chronically ill person who presents at initial examination relatively normal hemoglobin and red blood cell values. Presumably the blood loss during the operation cannot be compensated for by the inadequate ferrous stores of the malnourished person who as a rule is afforded a continued lower iron intake over his prolonged convalescent period. The importance of the greater adoption of hemogenic measures in the operative care of the patient becomes manifest. It has become the established rule in our service to attempt to elevate the hemoglobin level of patients to above 70 per cent by means of a hematinic diet in cases in which emergency operations are required in the face of readings of 60 per cent or lower, to administer three or more preoperative transfusions of 500 cc. of whole blood at appropriate intervals and to follow the operation by at least two additional administrations of 0.5 liter of blood. The common practice of giving one transfusion temporarily to bolster up reduced hemic components does not to our mind constitute more than a token acknowledgment of the frequently existing marked depletion of the body's hemopoietic reserves. The formula of Marriott and Kekwick here quoted may prove serviceable in determining the total required volume of blood necessary to correct a given degree of anemia. The blood volume may roughly be expressed as 40 cc. per pound (0.5 Kg.) of body weight.

$$\frac{\text{Percentage of rise of hemoglobin required}}{100} \times \frac{\text{Patient's normal blood volume}}{\text{in cubic centimeters}}$$

The acute anemia induced by the operative hemorrhage characteristic of radical resection is a strict indication for prompt and relatively rapidly given transfusions of whole blood. Rapid loss of blood in amounts exceeding 30 per cent of the total volume to 1.5 liters may prove fatal, and 40 per cent of the volume lost in producing shock must be immediately restored. Secondary anemia due to hemorrhage from cancerous organs must not be neglected. When for less emergent restorative indications large amounts of blood must be given to elderly patients, the rate of transfusion must not be lost sight of, because, unlike solution of sodium chloride, the added volume does not rapidly leave the vascular system. As reported by Marriott and Kekwick, the amount of blood required for every 10 per cent or 10 mg. increase of hemoglobin in the average adult is about a pint (0.47 liter). When an increase of more than 33 per cent is desired, the transfusion should be done in two stages with an interval of two days between. In the average adult, 1 cc. per pound (0.5 Kg.) per hour is the most rapid rate at which citrated

blood can be given safely. The incidence of untoward reactions increases at faster rates. If cardiac or respiratory disease is present, the amount per hour should be cut in half to prevent pulmonary edema. The only absolute contraindication to transfusion is acute pulmonary edema.

However, in the patient with cancer the presence of nephritis, gastrointestinal or pulmonary hemorrhage, peripheral vascular disease, thrombophlebitis, or embolism calls for extreme judiciousness in the use of whole blood. The febrile reaction seen after transfusions requires no more than symptomatic therapy. The commonest grave complication of blood administration is the hemolytic reaction; this is often accompanied by shock and anuria. These must be watched for, and the merest suggestion of them demands the immediate discontinuance of the transfusion. These reactions are considerably diminished by the use of plasma, untyped and readily stored, which may be used effectively in the treatment both of acute hemorrhage and of shock, as described by recent investigators. Incompatibility, hemolysis, degeneration of stored blood (inhibited by isotonic solution of dextrose), particulate contaminants, pyrogens and an increase of potassium have been described as responsible for transfusion reactions. It appears that such recently advocated blood substitutes as isoagglutinin-neutralized universal blood, cross-matched ascitic fluid, desiccated or spray-dried or frozen plasma, resuspended as a concentrate if so desired, and serum are less productive of such reactions than their precursors.

Care of the Patient with Jaundice.—As previously indicated, the recent conclusion of Ravdin that a high protein dietary component equals in importance a high carbohydrate concentration in the protection of the liver has influenced the diets we give before and after operation. When possible, the usual recommendation to defer operation until the serum bilirubin is less than 20 mg. per hundred cubic centimeters should be heeded. However, since icterus of malignant origin is progressive rather than remittent as a rule, it is seldom that it may be taken to apply in cases of cancer. The carbohydrate requirement of approximately 500 Gm. daily cannot be entirely met by the 250 Gm. available in 2,500 cc. of 10 per cent solution of dextrose given intravenously. An additional supplement of 250 Gm. of carbohydrate as well as 100 Gm. of protein must be administered by other routes and, when necessary, by orojejunal feedings. Vitamin concentrates are doubly required since liver disease means impaired hepatic storage of at least vitamins A, B, C, D and K.

Several recent studies confirmed the impression that the newer vitamin K synthetics given in small quantities intravenously may be substituted for the natural derivative formerly administered; 3 mg. of vitamin K₁ or an equivalent naphthoquinone is given daily, one dose the day before, and one after the operation. The response, poor in the presence of severe damage to the liver, occurs with a rise in blood pro-

thrombin levels within two hours. Transfusions, at least one preceding and following operation, are continued as heretofore, and in effect augment action of the vitamin K. Bleeding and coagulation times, simpler to obtain than prothrombin determinations in a municipal hospital, although the latter are preferable, are taken twice preoperatively and once postoperatively. Reed found that large amounts of extract of adrenal cortex favor a 30 per cent increase in the coagulation rate of the blood. Apparently this effect obtains even in the presence of cholecystitis and mild icterus. Weir and Collier proposed that ineffective prothrombin response to the administration of vitamin K serves as an indicator of hepatic injury.

The relation of vitamin K deficiency to cancer has of late assumed added interest in view of the experimental work of Fieser, who demonstrated a protective mechanism against methylcholanthrene carcinogenesis in mice associated with the administration of vitamin K and elevation of blood prothrombin. In a small series of blood prothrombin determinations, however, we have failed to find blood prothrombin deficiency a characteristic concomitant of all forms of cancer, although Fieser's observations indicated that possibility. A more complete survey of this matter will be presented at a later date. The fact that prothrombin levels fall rapidly after restoration with vitamin K emphasizes the necessity for prolonged therapy.

Thrombosis and Embolism.—Cardiac disease, since it predisposes to congestive heart failure, circulatory insufficiency and venous stasis, and the peripheral vascular diseases frequently met with in the middle aged are responsible for the somewhat increased tendency to thrombosis and embolism seen postoperatively in patients with cancer. These complications, when they occur, are apt to become evident from the fifth to seventh day of convalescence, but grave attacks generally occur on the tenth day, according to Westdahl. When the clinical condition of the patient seems to indicate such measures, particularly in cases in which pelvic operations are to be done, when the risk of thrombosis is known to be greatest or when a second embolus is to be prevented, the use of heparin as a preventive measure may be warranted. This is suitably administered as 30 cc. (60,000 anticoagulant units) of heparin solution added to a liter of venous infusion fluid daily at a flow rate of 25 drops per minute for four to ten days. The clotting time of venous blood should be kept at a level between fifteen and twenty minutes. This obviates the danger of excessive bleeding. Several hours after heparin stoppage, coagulation times become normal. De Takáts discussed the role of hemoconcentration and shock in leading to thrombosis.

Potts and Smith showed an increase in volume of blood flow in the inferior vena cava after deep breathing and leg exercise. Prevention of venous stasis in the lower extremities is the crux of the prevention of

pulmonary embolus. To combat phlebitis when large vessels have been manipulated, patients are urged to move about early in convalescence. Frykholm stated that elevating the head of the bed (Fowler position) for 1 or 2 hours daily encourages lower limb activity and prevents thrombosis. He recommended daily palpation of the sole, the calf and the thigh for tender areas. Westdahl concurred in this viewpoint. It is our impression that the beneficial effects on neurovascular and muscular tone obtained by having the patient active and out of bed, when feasible, for several days prior to operation also serves to prevent thrombosis. That continuous intravenous infusion, particularly when one vein has been used time after time, produces thrombosis in the veins of the upper or lower extremities, as the case may be, is another common experience. Culp pointed out that when thrombosis is suspected routine daily measurements of the leg circumference from the malleoli upward may lead to early recognition and that by enforcing prolonged rest in bed in these instances one may possibly forestall pulmonary embolism. Walters expressed the opinion that thyroxin, by increasing the rate of circulatory flow, is of specific value in the prevention of postoperative pulmonary embolism. It is hardly to be expected that patients with cancer with massive pulmonary emboli after extirpative procedures could be considered as candidates for drastic pulmonary vein operative interventions. Patients surviving this complication long enough to receive any treatment seem to improve somewhat after the use of papaverine in large doses used simultaneously with helium-oxygen therapy. Sears advises ligation of the femoral vein when postoperative thrombophlebitis, often revealed only by persistent pain in the calf, is recognized for the prophylaxis of postoperative pulmonary embolism and for the prevention of recurrence if initial embolization has been survived.

Respiratory Complications.—Under the heading of infections, a brief discussion of the prevention and treatment of postoperative pneumonia will be presented. The larger aspects of the problem of postoperative pneumonopathies are probably best considered in relation to the predominantly mechanical phases concerned prior to the onset of actual pneumonitis.

Several recent collective reviews corroborated the generally held impression that atelectasis is the predominant postoperative pulmonary complication. Massive lung collapse represents an extreme and grave phase of this condition, and from it stems also postoperative pneumonia, according to the newer concepts. In cases of postoperative bronchitis, pneumonitis and lung abscess, infection, frequently autogenic, assumes the dominant role over the previously mainly operative mechanical factors. Pulmonary embolism and infarction are more properly categorized as vascular accidents.

People of 50 years of age or over, leading an enforced sedentary existence over a prolonged period and with early cardiac and pulmonary degenerative disease, such as arteriosclerotic heart disease and initial emphysema, have limited vital capacities at best. The added strain of temporary circulatory and respiratory embarrassment attendant on any major anesthetic and surgical procedure leads to some degree of hypostatic congestion and hypoventilation in every patient with cancer during and after the operation. It is precisely these two physiologic disturbances that favor atelectasis and that must be overcome to minimize the incidence of this complication. Hypoventilation is chiefly due to pain and reflex spasm, but it originates also to some degree from the decreased tonus of the muscles and nerves involved in inspiration and expiration which may follow actual operative trauma, as after procedures in the upper part of the abdomen lessening diaphragmatic mobility. Reflex circulatory disturbances of a magnitude to produce some degree of pulmonary stasis is the usual occurrence in major abdominal or thoracic resections, and these coupled with hypoventilation result in relative anoxemia.

The character of the bronchial content requires attention in this regard. The concept of Coryllos and other workers that a thickened inspissated mucous plug effectively obstructs a bronchial or bronchiolar passageway, resulting as air absorption is completed in lobar, segmental or scattered lobular atelectasis, as the case may be, suggests another important avenue for prevention and therapy. These nonfunctional consolidated areas are rapidly invaded by micro-organisms normally found in the upper respiratory passages with the picture shortly becoming that of pneumonitis. Since the temperature may by reflex disturbance be elevated before pneumonia supervenes, fever cannot be accepted as a reliable differential diagnostic sign between pulmonary infection and atelectasis. In general, roentgen evidences of diminished lung aeration during the first thirty-six to forty-eight hours should be interpreted as atelectatic phenomena. Since prompt prophylactic procedures against pneumonia must be instituted, there is little significant difference in therapy between the two at this stage. To return to the matter of bronchial secretions, Gordon suggested the possible harmful effects of the indiscriminate preoperative prescription of atropine to diminish them, holding that bronchial obstruction is favored by the resultant thickened viscid mucus secreted. Numerous observers have stressed the hazards of neglecting the stuporous patient, whose normal cough and other removal mechanisms are suspended for several hours immediately after the operation, when thick nasopharyngeal secretions or aspirated vomitus or blood may accumulate in the tracheobronchial tree. A further reason for routine use of the Trendelenburg position in the unconscious patient is the postural drainage it affords.

All too often the admonitions to change the position of the patient frequently and to avoid excessive narcotization are overlooked by the

busy resident and nursing staff. Feeling that to neglect these precautions is particularly hazardous in our type of patient, detailed instructions for the proper handling of each patient in this regard are given. Hyperventilation is encouraged by carboxygen inhalations, and instructions for deep breathing and periodic coughing exercises are outlined. Although no noncontroversial evidence as to the relative advantage of any of the opium derivatives over morphine in depressing the activity of the respiratory center has been presented to date, the recommendation of Harrington and others to supplement small analgesic dosages of morphine with codeine and barbiturate sedatives or prostigmine synergism is followed. The anesthetist, before returning the patient from the operating room, often clears the airway by thorough bronchial suction via catheter. Bedside chest plates are routinely ordered and in the presence of dyspnea, cyanosis, thoracic pain and fever are repeated at intervals.

Minor degrees of atelectasis, once established, may be treated by vigorous application of the measures already described. The patient is instructed to cough and breathe deeply and is given continued administrations of mixtures of carbon dioxide and oxygen. Vigorous percussion over the affected lobe as the patient in the Trendelenburg position coughs with attempts to expectorate is a manipulation which several times seemed to yield good results when we carried it out. More severe forms of atelectasis respond best to emergency bronchoscopic aspiration of obstructing mucus. Coramine, caffeine, metrazol and similar preparations may be judiciously administered to stimulate respiratory activity and are of especial value in counteracting hypoventilation secondary to the use of large doses of analgesic or sedative medicaments. Care must be taken also to avoid unnecessary constriction of the lower ribs and the abdomen by dressings or restraints. As is obvious, uncontrolled abdominal distention, by increasing the patient's dyspnea, is an important contributory factor in the development of pulmonary disturbances.

Intrathoracic surgical procedures require careful postoperative control of intrapleural pressures. Routine readings are carried out at the close of the operation and checked frequently at the bedside. To obviate the possibility of tension pneumothorax, a tube or a large bore needle introduced intercostally is attached to a water-sealed gravity suction apparatus, as described by several thoracic surgeons. Negative pressures in excess of 20 mm. of mercury are avoided lest intrathoracic hemorrhage and exudate be increased. The advice of Alexander to prevent the paradoxical motion of the thoracic wall by elastic compressive dressings and by having the patient lie on the side operated on is heeded. In this manner thoracic shock associated with cyanosis, rising pulse, shallow breathing and falling blood pressure secondary to the transmission of the paradoxical motion to the mediastinum is rendered less likely.

In all conditions in which respiratory difficulty is anticipated this administration of oxygen to lessen anoxemia is carried out. If acapnia or hypoventilation occur, 6 per cent carboxygen for periodic inhalation is given. Marked dyspnea is, in our experience, seldom completely relieved by the customary tent atmosphere of 60 per cent oxygen. It is our impression that the oxygen tent is best indicated when some form of air conditioning is as important as added oxygenation. Thus, in extremely hot weather, the controllable temperature and humidity of an oxygen tent can be utilized to forestall excessive perspiratory fluid and electrolyte loss. Likewise, the pneumonic patient with hyperthermia may do well in the coolness of the tent. However, it is often lost sight of that the status of patients susceptible to shock may be seriously aggravated by chilling.

The recommendation of the surgeons at the Mayo clinic that 100 per cent oxygen be administered by face mask, when needed, for periods up to forty-eight hours seems to work out well in patients showing marked respiratory difficulty. Their recent studies on mixtures of oxygen and helium, indicating that this lighter than air combination diffuses in the lung alveoli into the blood with a minimum of physical respiratory effort, suggest that the necessary equipment is indispensable in the armamentarium of hospitals seeking to give the best of modern operative care. With mixtures of oxygen and helium at a pressure of 6 mm., in which the former is kept above 20 per cent and the use of a Boothby-Lovelace-Bulbulian mask as described by its originators, sufficient oxygenation to sustain life with little breathing motion on the part of the patient can be maintained. This has proved of considerable clinical value in the treatment of shock and postoperative pulmonary complications, especially pulmonary edema, and seems to be of some worth in the relief of severe abdominal distention.

Infections (Pneumonia, Peritonitis, Wound Healing).—As has already been emphasized, the essence of prevention in hypostatic and atelectatic pneumonia depends on combating the more or less mechanical processes responsible. The relative merits of spinal and intravenous anesthetics over those of the inhalation type are not as yet established. It is our practice to choose an anesthetic suited to the requirements of the patient in consultation with the physician anesthetist, whose specialized knowledge and experience in the field insure a more logical choice. A synergistic combination of $1\frac{1}{2}$ grains (0.09 Gm.) of soluble pentobarbital given two hours, and $\frac{1}{6}$ grain (0.01 Gm.) of morphine sulfate plus $\frac{1}{200}$ grain (0.03 mg.) of scopolamine hydrobromide one and one-half hours, preoperatively is administered in the average case. Doses are adjustable according to body weight. Cyclopropane (intratracheally, if a closed system is required), spinal procaine-nupercaine mixtures,

intravenous sodium pentothal and local procaine infiltration are the anesthetic agents we most often use, in about the order of frequency listed.

In experimental studies with animals, Pickrell found that during anesthesia and for a variable interval thereafter, the immune functions of the organisms are suspended. The inflammatory response is delayed until the period of effective drug action is over, possibly a matter of four to six hours, during which bacterial invasion is observed to proceed unchecked. During this period, in which the body defenses are at a demonstrably low ebb, the pathogenic micro-organisms of the nasopharynx or the colon may gain sufficient impetus to withstand the inflammatory protective processes once they do get under way. This focuses a new light on the causative *modus operandi* of postoperative pneumonia and peritonitis and adds another reason for avoiding prolonged periods of anesthesia, particularly in the debilitated or elderly sufferer from cancer. Both before and after operation, rigorous attention to oral and nasopharyngeal hygiene is therefore of importance. If need be, consultation with regard to the dental and the nose and throat condition should be requested. Infected gingival pockets, paranasal sinus discharges and the sordes so commonly seen in dehydrated chronically ill patients may serve as prolific sources of the secondary bacterial invaders of otherwise low pathogenicity that may gain a septic foothold. Chronic bronchitis, bronchiectasis or emphysema, as the case may be, widely prevalent in patients past 50, is deserving in every instance of careful thought. The powers of resistance to bacterial invasion of the patient at the cancer age should in general be considered as in decline, and the comfortable assumption, warranted in general surgical practice, that a youthful vigorous patient may readily check the renewed onslaughts of the microbic residents after the usual operative insults to the body defense mechanisms should never be allowed to color the judgment of the cancer surgeon.

With regard to the prevention of pneumonitis by chemotherapy, we have felt, as have others, that the prophylactic dose should be estimated as equivalent to the therapeutic dose, pending conclusive studies establishing adequate criteria of the preventive dose for human beings. Fuller lately stated, however, that half doses and blood levels for four or five days may be adequate in the prophylaxis of wound infections. Recently, in view of the comparably low toxicity and the fact that sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) has been repeatedly reported as an effective bacteriostatic agent against pneumococcus and *Streptococcus haemolyticus* as well as staphylococci, we have adopted it for routine use to forestall infection when anticipated. Studies demonstrating its effectiveness against the typhoid colon bacillus, *Streptococcus faecalis* and enterococci group of organisms have led us to feel that it

may be of value as a prophylactic against peritonitis, genitourinary and wound infection as well as pneumonitis, although the encouraging results in the small group of cases in which we have employed sulfathiazole to date cannot be considered as conclusive evidence in its favor. Soluble preparations, such as sulfathiazole sodium sesquihydrate, may be used intravenously. Blood studies to guard against hemolysis, icterus, anemia and neutropenia and examinations of the urine for hematuria or anuria are carried out routinely. In the event that serious toxic reactions occur, the drug is promptly discontinued, and fluids are forced.

Not infrequently enteroanastomosis contraindicates the oral administration of sulfathiazole, and recourse to other methods, as intraperitoneal deposition of doses of 8 grains (0.52 Gm.), is required. Here the more soluble sulfanilamide and sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) may be substituted by subcutaneous infusion if required. When a Miller-Abbott or a duodenal tube is being used, the drug may be given by this means. An 0.8 per cent solution in physiologic solution of sodium chloride is administered at the rate of 2 cc. per pound (0.5 Kg.) of body weight every eight hours. Rectal administration as a 1 per cent solution of one to two times the oral dose, regulated by blood readings, is seldom resorted to. With all of these drugs, particularly sulfathiazole, fluids must be forced to prevent the formation of obstructive ureteral crystalline deposits. Sulfadiazine (2-[paraaminobenzenesulfonamido]-pyrimidine) in equal doses is possibly less toxic and may be given in the presence of liver or kidney damage.

Peritonitis, according to various workers, may be reduced in incidence by the use of intraperitoneal vaccines, sodium ricinoleate, serum immunotransfusions and other measures. Other than the use of sulfanilamide and its derivatives and radiation therapy, we have had little experience in the use of these methods. Recent reports by such surgeons as Rankin and Graham, who have had extensive unconvincing experience with various plans for peritoneal immunization, seem to arouse doubt as to their worth. Firor's recent work on the use of sulfaguanidine (sulfanylguanidine), in doses of 0.05 Gm. per kilogram of body weight every eight hours, for a week before and after operation seems promising.

Wound infections, we feel, are kept at a minimum by the general program aimed at restoring the patient to optimum physical condition and rigid asepsis. However, the value of several recent local therapies is sustained in our experience. First dressings are usually made after two or three days. In recognition of the delayed healing powers often dealt with, sutures are removed in from seven to twelve days. Infected wounds, particularly those in which radiation changes are present and further inhibit the healing processes, are packed and dressed, after saline irrigation, with gauze impregnated with zinc peroxide cream as advo-

cated by Meleney, Reicher, Freeman and Sunderland or painted with 2 per cent aqueous gentian violet solutions. Irrigations with azochloramid in a concentration of 1:2,500 in saline solution or dressings with this compound in a concentration of 1:500 in triacetin are frequently used with good results. The paper by Johnson on the value of azochloramid preparations when bacterial contamination leads one to anticipate wound infection and in speeding healing despite the presence of actual wound infection seems to be well founded. Of late we have been using sulfanilamide, sulfapyridine and sulfathiazole, especially the first since it is more soluble, in the form of crystalline powder dusted liberally over the wound surfaces as a local bacteriostatic agent, following the recommendation in several suggestive reports. A 10 per cent solution of sodium sulfate has been advocated for infected wounds by Lyth. Adhesive approximations and gauze packing may prove less shocking than immediate resuture in wound disruptions.

That the patient with diabetes requires careful preoperative preparation is well recognized. The details of such preparation are not within the scope of this paper. However, a recent warning by Eschweiler may well be repeated, namely, that the routine practice of covering 500 cc. infusions of 10 per cent solution of dextrose by 25 units of insulin may precipitate hypoglycemia. Insulin shock is a grave complication in chronic invalids and aged patients. A moderate glycosuria in the absence of ketosis is preferable to the risk of postoperative insulin reactions or coronary thrombosis, precipitated by hypoglycemia, in the elderly. Carbohydrate-insulin balance is left in the hands of the medical service prior to the operation. Immediately before operation and at four hour intervals after operation blood sugar and carbon dioxide determinations should be made. Ordinary insulin is preferable because it is easier to administer than protamine or protamine zinc insulin preparations during this period, and the usual amount may have to be increased because of the relatively high carbohydrate intake given. The procedure of Terry, who recommended 15 units for a red, 10 units for a yellow and 5 units for a green precipitate in four hour urine specimens, increased as required in the presence of acetone bodies, is a suitable routine for postoperative care when blood for chemical analysis cannot be obtained. Normal wound healing may be expected in a nonketotic patient with moderate glycosuria and hyperglycemia. Finally, it should not be lost sight of that ketosis is much more easily forestalled than insulin shock.

SUMMARY

A review of contemporary advances and an analysis of our experiences with relevant current clinical procedures in the preparation for operation and postoperative care of patients at a municipal cancer hos-

pital are presented. The following factors, of specific significance in surgical procedures for malignant tumors, have been given special consideration:

1. The patient with cancer should in general be considered chronically ill. By the usual standards a relatively poor surgical risk, he is a candidate for radical operation and therefore requires the most diligent supportive preoperative and postoperative care.

2. That some degree of arteriosclerotic heart disease exists is a reasonable assumption in the average patient with cancer. Relative circulatory inefficiency renders congestive heart failure, shock, thrombosis, embolism and hypostatic pneumonia major surgical risks. The routine use of electrocardiography and chest plates is therefore of particular value in the treatment of patients with cancer. Impaired renal and hepatic function, diminished vital capacities, obesity, diabetes, hypertension and vesical retention are likewise frequent concomitants of cancer that must never be overlooked. These require intensive corrective preoperative preparation.

3. Among 100 consecutive unselected patients admitted to the surgical service at Brooklyn Cancer Institute, the total serum proteins averaged below 6.5 mg. in 55 per cent. The carbon dioxide-combining power was found to be under 53 in 58 per cent. The presence of acidosis, ketosis and hypoproteinemia may therefore be considered presumptive in the average patient with cancer. Hypoproteinemia is an index of malnutrition. Malnutrition invariably presupposes the existence of surgical avitaminosis. Hypoproteinemia likewise predisposes to shock, edema and great impairment of wound healing.

4. The average whole blood chloride level on admission to our service was below 450 mg. in 45 per cent of the cases. Particularly in cases of gastrointestinal neoplasm, fluid electrolyte imbalance is a safe general assumption. Except in the presence of electrolyte loss, the routine use of dextrose-saline mixtures will often yield a daily surplus of 20 Gm. of sodium chloride, an amount possibly transcending the excretory function of the kidneys of the middle-aged patients. The clinical rules of Maddock and Collier for water and salt balance have proved satisfactory in our service. Prolonged suction drainage by a Levine or a Miller-Abbott tube, whether or not fluids and salt are given orally, requires volume for volume parenteral administration, since the enteric secretions drawn off are isotonic, while absorption of water and salt appears to take place mainly in the colon. Uncorrected hypoproteinemia, anemia and total base loss have been shown to be associated with little understood disturbances of water and sodium chloride absorption, retention and excretion. A greater incidence of serious surgical problems in water-electrolyte balance may therefore be anticipated in a series of cases of cancer.

5. The real threat of overtaking the circulation and precipitating pulmonary edema or congestive heart failure must be borne in mind when infusions or transfusions are administered to a middle-aged patient.

6. The patient with cancer has a greater susceptibility to shock because of lowered serum proteins, degenerative changes and anemia as well as the magnitude of the operative procedures. Hematocrit readings and determinations of plasma protein and specific gravity are thus particularly indicated in prevention. Prevention is of paramount importance because advanced shock is generally irreversible. Attempting to combat shock by administration of dextrose-saline solutions is to confuse the problems of shock and fluid-electrolyte balance. Prompt administration of plasma or blood is of greatest avail.

7. Anemia is a well recognized characteristic of patients with cancer but is all too seldom corrected prior to operation. The average hemoglobin content of 65 of the 100 successive patients entering the hospital was below 65 per cent. Uncorrected anemia predisposes to shock, edema and poor wound healing and implies from the outset the handicap of relative tissue anoxia.

8. Postoperative pulmonary complications may be expected to be more common among patients over 50, the age when initial emphysema, coronary sclerosis and chronic bronchitis are commonly seen. Anesthesia and operative procedures must not be unduly prolonged for this reason. Neglect of detailed preventive precautions in this age group may often mean the failure of an otherwise successful procedure.

9. Immediate operation on the patient with cancer without intensive preoperative preparation and postoperative care based on the specific requirements of this group courts an often avertable disastrous end result.

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ABSORPTION OF SURGICAL GUT (CATGUT)

I. THE DECLINE IN TENSILE STRENGTH IN THE TISSUES

HILGER PERRY JENKINS, M.D.

AND

LEO S. HRDINA

CHICAGO

The absorbability of surgical gut (newly adopted U. S. P. term to designate sheep intestine prepared for surgical use, instead of the misnomer "catgut") has been a somewhat controversial subject. One of the purposes of this work on absorbability was to ascertain the decline in the tensile strength in the tissues of plain and chromic catgut available from different manufacturers. In 1928, Howes¹ reported his observations on the loss of strength of catgut when embedded in the tissues. The most complete review of earlier studies on catgut was presented by Rhoads, Hottenstein and Hudson² in 1937 along with clinical and experimental observations on the decline in the strength of catgut after exposure to living tissues. Further clinical studies on the loss of strength of catgut also were published that same year by one of us (H. P. J.).³ In 1939, Wolff and Priestley⁴ made a comprehensive report on the duration of tensile strength in the tissues of patients for various sizes and types of catgut available from six different manufacturers. In the latter two reports, it was generally found that the behavior of the catgut in the tissues from the standpoint of the duration of tensile strength did not correspond closely with the labels of twenty day chromic or forty day chromic, which were generally in use at that time to designate the "approximate" absorption time of the catgut.

From the Department of Surgery, the University of Chicago, the School of Medicine.

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METHOD

The decline in tensile strength was studied by a series of 1,500 implants of surgical gut (catgut) in the abdominal muscles of dogs. The standard products of ten companies were subjected to tests. The plain, twenty day or medium hard chromic and the forty day or extra hard chromic catgut from six companies in the various sizes of no. 2 to no. 000 were used. The twenty day, or medium hard, chromic catgut of four other companies was tested in the sizes of nos. 2, 0 and 000. Most of the gut used in these tests was manufactured prior to the change in labeling recommended by the Committee of Revision of the United States Pharmacopeia; hence it will be referred to as catgut. To avoid confusion the following schema represents the new nomenclature and what is presumed to be the equivalent formerly in use.

Official U. S. P. Terminology	Terminology Formerly in Use
Type A: Plain surgical gut (untreated)	Plain catgut
Type B: Mild chromic surgical gut (mild treatment)	Ten day chromic catgut
Type C: Medium chromic surgical gut (medium treatment)	Twenty day chromic catgut; medium hard chromic catgut, ten to twenty day
Type D: Extra chromic surgical gut (prolonged treatment)	Forty day chromic catgut; extra hard chromic catgut, thirty to forty day

The operative procedures were carried out on the animals with careful aseptic technic while they were under ether anesthesia. The implants were made with the aid of a long flexible probe at one end of which was an eye through which a 6 inch (15 cm.) length of catgut was threaded. The probe was inserted through a small incision in the upper part of the abdomen into the abdominal muscles and then carried down to the lower part of the abdomen, where a second small incision permitted withdrawal of the probe. When the probe was almost completely withdrawn, the catgut strand was released from the eye of the probe by traction at the upper end of the strand, thus leaving the catgut buried in the muscles. Any excess catgut which extended out through the incision was cut off, and the free ends were replaced deeper in the tissues. The incisions were then closed with fine silk.

Most of the implants were made in duplicate by using a portion of the same strand of catgut in 2 different animals operated on simultaneously. The remaining unused portion of catgut was saved, moistened to permit pliability and then hung up to dry with 30 to 70 Gm. lead weights tied on the end to maintain tension. After thorough drying, the average diameter was determined from several readings with an instrument graduated in thousandths of an inch (0.0025 cm.). A portion of the catgut was used for testing the tensile strength, which is hereinafter mentioned as the original tensile strength. A spring scale graduated to $\frac{1}{4}$ pound (113 Gm.) was used for these tests. The remaining portion of the catgut strand was saved for digestion tests in enzyme solutions, the results of which will be reported subsequently.

It was usually feasible to implant three to five strands of catgut on each side of the abdomen, depending on the size of the animal. The animals were killed

at the end of various periods, depending on the particular catgut used in the tests. For example, a chromic catgut test might be terminated in 1 animal in seven days, while the duplicate implants in another animal might be permitted to remain for ten days. The plain catgut tests were usually terminated at the end of three, five or, in some instances, seven days. Some of the chromic catgut tests were not terminated until fifteen days. Various combinations of catgut were used in different animals. For example, a certain size of twenty day chromic catgut of six different companies was used in duplicate animals until all sizes had been checked. Then each size of twenty day chromic catgut of one company was matched against each size of the supposedly comparable product of another company. Also, the twenty day chromic catgut of one company was checked against the forty day chromic of the same company. In this way it was possible to have a diversified grouping of the various catguts. In some of the earlier series, the tests were conducted by implanting several different sizes of the same kind of catgut in the same location so that the strands of various sizes were subject to identical amounts of tissue reaction.

After the animal was killed, the abdominal wall was dissected to recover the catgut implants. In some instances, the catgut was in such a state of disintegra-

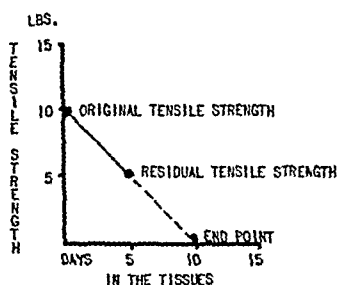


Fig. 1.—Showing graphic method of determining duration of tensile strength of catgut in the tissues.

tion that it could be removed only as fragments or shreds. The intact strands of catgut were removed and hung up to dry. Subsequently a determination of the tensile strength was made, which is referred to hereinafter as the residual tensile strength. Observations were made of the tissue reaction about the various implants. In some series, a specimen of tissue and catgut was taken for microscopic studies. These observations will be discussed in subsequent communications.

In order to make reasonable comparisons of the behavior of different kinds of catgut, it was necessary to express the various observations made in terms of days of duration of tensile strength. Computations of the theoretic end point at which useful holding power is gone can be made either by equation or graph from determinations of the original tensile strength, the residual tensile strength and the number of days the catgut was in the tissues. This is based on the assumption that the decline in tensile strength of catgut in the tissues is a relatively constant factor.

This assumption is supported by work of Howes¹ and of Rhoads and co-workers² as well as by observations made during the course of these experiments. For

example, a strand of catgut with an original tensile strength of 10 pounds (4.5 Kg.) may be implanted in a dog for five days. When removed after this period in the tissues, it may be found to have a residual tensile strength of 5 pounds (2.3 Kg.). It has lost 50 per cent of its original tensile strength. This is equivalent to approximately 10 per cent a day. At the end of ten days it would presumably have undergone complete loss of tensile strength. Although the decline in tensile strength of catgut in the tissues may not always be an absolute constant, it is at least sufficiently uniform to afford a reasonable basis for

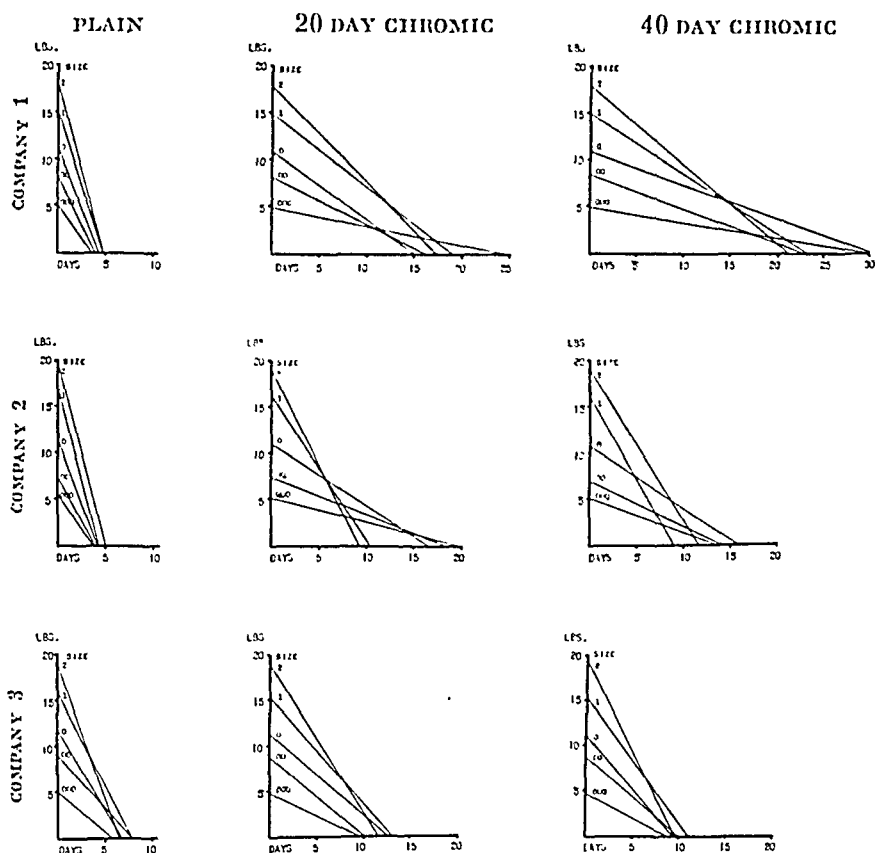


Fig. 2.—Graphs showing decline in tensile strength of catgut in the tissues of dogs (series 1939-1940).

expressing the various observations made in terms of days of duration of tensile strength.

Graphically, the decline in tensile strength can be plotted by drawing a straight line between the points representing original tensile strength and residual tensile strength on the day the catgut was removed. By projecting this downward, it will be found to intercept the base line at the theoretic end point, which represents the expected duration of tensile strength in days. This method is demonstrated in figure 1.

The following equation appears to cover the situation:

$$\frac{T \text{ (original tensile strength)}}{T - t \text{ (original less residual tensile strength)}} \times D \text{ (days in the tissues)} = E \text{ (theoretic end point)}$$

It is obvious from the aforementioned equation and graph that appreciable errors can be obtained from relatively slight inaccuracies in the determination of the original or the residual tensile strength, especially when the loss of tensile strength is relatively slight over a short period. This source of error was taken into consideration, and calculations which resulted in rather dubious end points were either discarded or corrected.

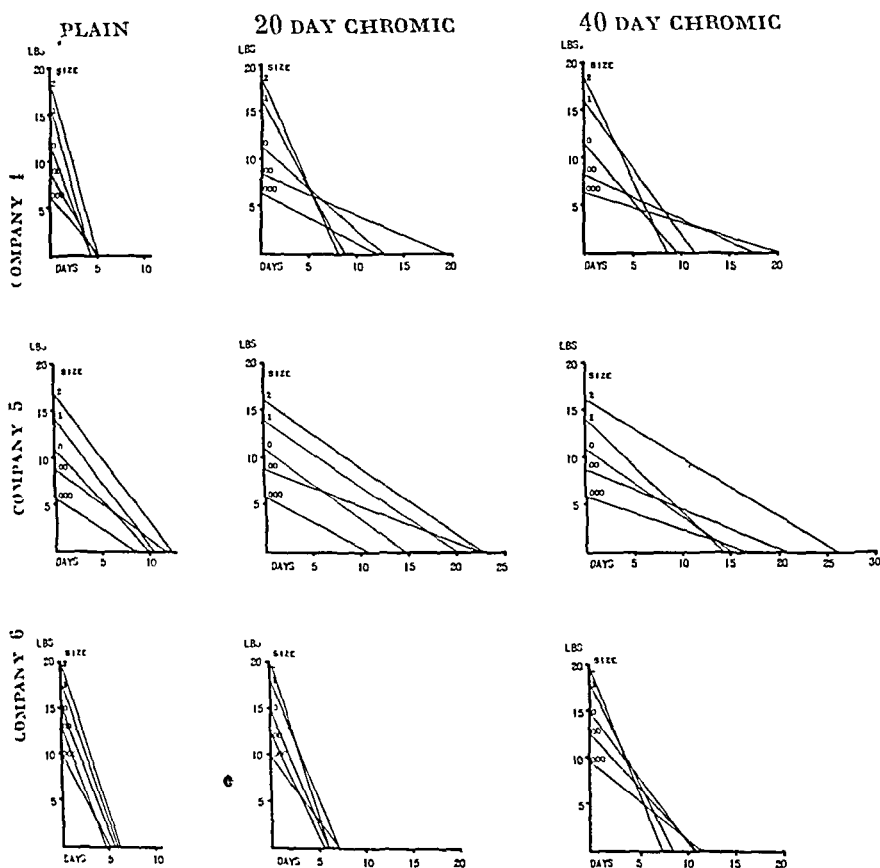


Fig. 3.—Graphs showing decline in tensile strength of catgut in the tissues of dogs (series 1939-1940).

When autopsy revealed that certain strands of catgut were sufficiently disintegrated that only short fragments could be recovered, it was assumed that this represented the end point for this particular catgut. The duration of tensile strength was then computed as the number of days between implantation and autopsy. If the catgut could be recovered only in the form of small shreds, it was considered that the end point had been exceeded by a half day.

After transposing all the observations into terms of days of duration of tensile strength, an average was obtained for each size, kind and brand of catgut. The results are presented in the form of graphs showing the decline in tensile strength

from the average original tensile strength on the day of implantation to the end point when the tensile strength would be negligible on some particular day after implantation.

The first series of graphs (figs. 2, 3 and 4) represents the results obtained from the catgut purchased from ten different manufacturers during 1939-1940.

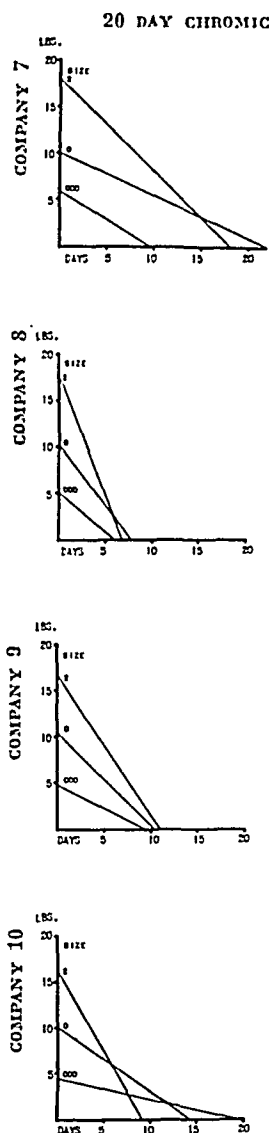


Fig. 4.—Graphs showing decline in tensile strength of catgut in the tissues of dogs (series 1939-1940).

The next group of graphs (figs. 5 and 6) represents observations on catgut obtained for the most part during 1938. The third series of graphs (figs. 7, 8, 9 and 10) compares the results of tests conducted on dogs with clinical tests made on patients. The catgut used for this was acquired to a large extent in 1937,

although some results were incorporated into these charts which were based on catgut obtained prior or subsequent to this date. To avoid confusion the results are grouped into three main series representing approximately the work done during those years.

Regarding the graphs showing the decline in tensile strength of catgut in the laparotomy wounds of patients, the results shown were based on the average duration of tensile strength of each particular catgut as determined by the tension suture test. This was fully described in a previous publication.³ The end point

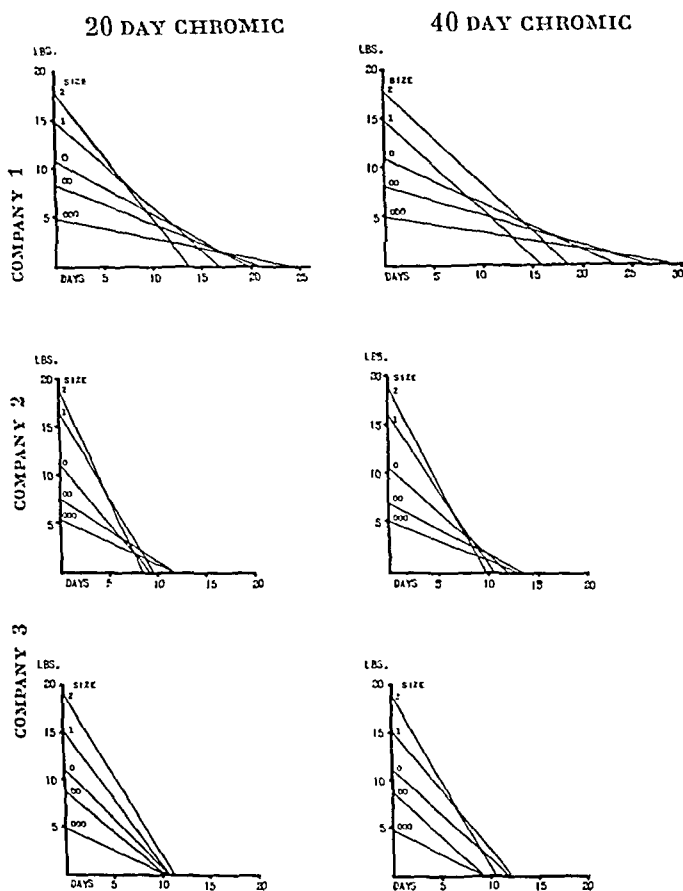


Fig. 5.—Graphs showing decline in tensile strength of catgut in the tissues of dogs (series 1938).

was considered as that day on which the catgut tension suture could be lifted out of the wound with relatively little tension because of practically complete loss of tensile strength of the catgut exposed to the action of the tissues. In instances in which it was desirable to terminate the tests at the end of twelve to fifteen days on certain types of more slowly absorbed catgut, the loop of catgut was cut near the knot which was outside the tissues, and then the strand was lifted out. It was subsequently dried and subjected to a test for residual tensile strength. Then a computation of the theoretic end point was made by either the formula or the graphic method, taking into consideration the original tensile strength and the duration of the catgut in the tissues, as well as the residual strength.

RESULTS

It can be observed from the three series of graphs that the general behavior of the plain and the chromic catgut of the various companies tested over a period of three years was to a certain extent relatively consistent. On the other hand, appreciable changes in the behavior of some of the brands of chromic catgut did occur.

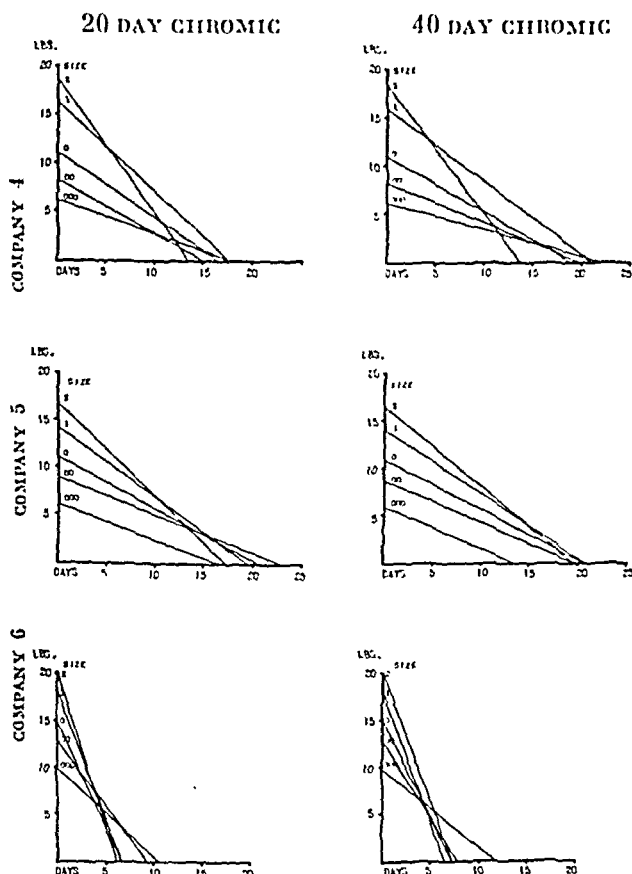


Fig. 6.—Graphs showing decline in tensile strength of catgut in the tissues of dogs (series 1938).

Plain catgut was usually found to undergo complete loss of tensile strength within approximately five days. In a few products, the duration of tensile strength was between five to eight days, and in 1 instance, eight to twelve days.

Chromic catgut showed considerable variation in its performance. In general, it was observed that differences between twenty day and forty day chromic catgut of the same company were relatively slight as compared to the rather striking inconsistencies between the chromic catgut of different manufacturers.

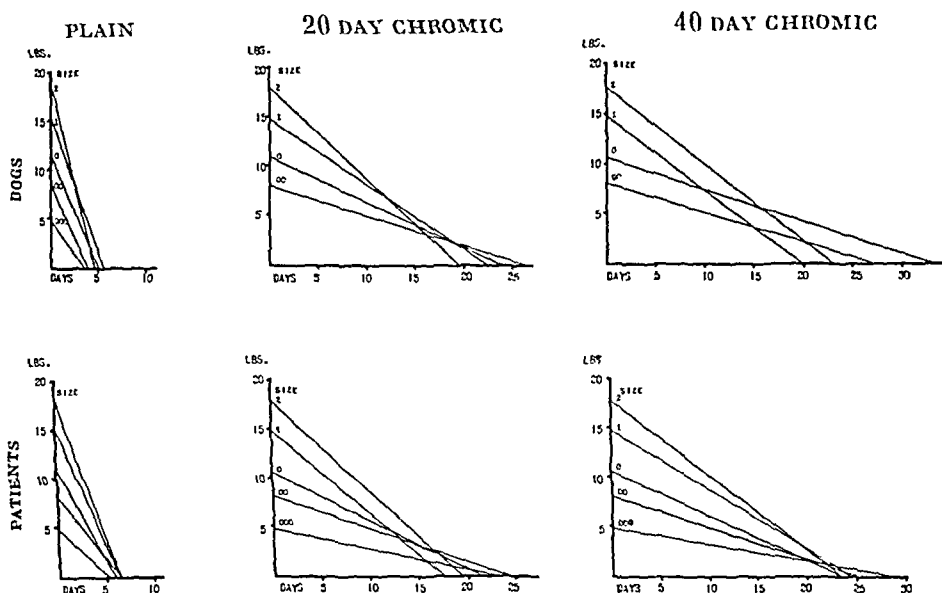


Fig. 7.—Graphs showing decline in tensile strength of catgut in the tissues of dogs as compared with that observed in patients (series 1937; company 1).

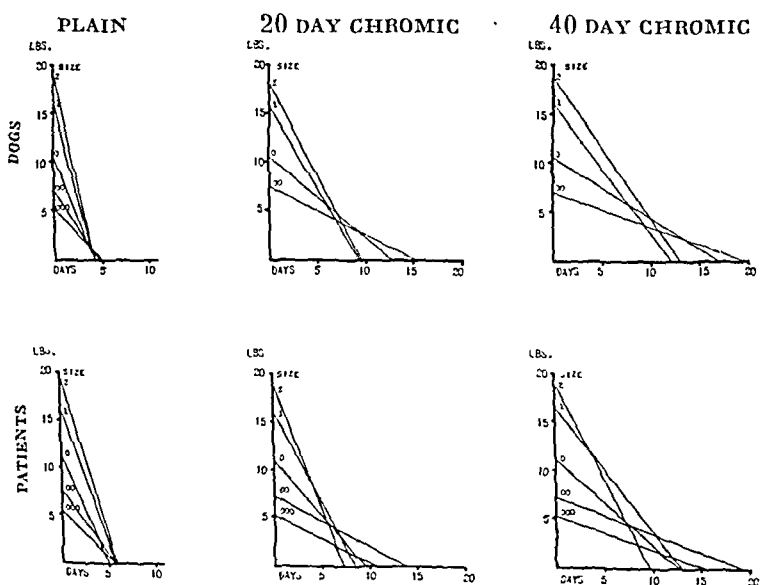


Fig. 8.—Graphs showing decline in tensile strength of catgut in the tissues of dogs as compared with that observed in patients (series 1937; company 2).

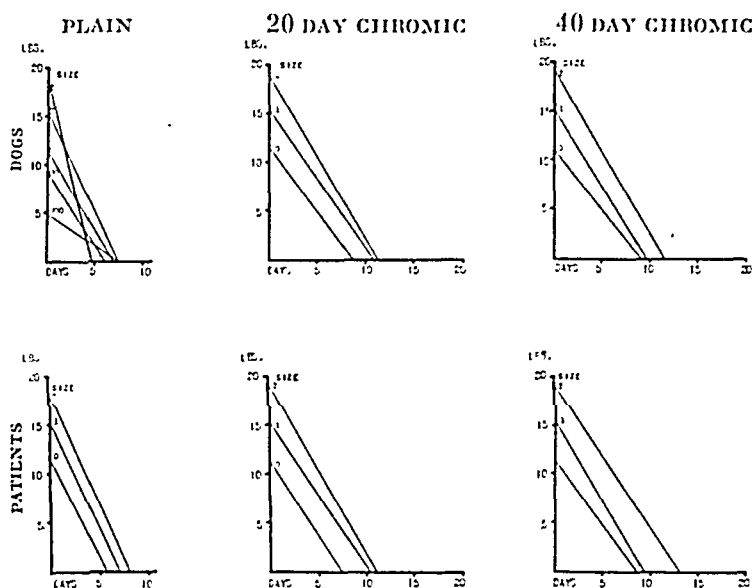


Fig. 9.—Graphs showing decline in tensile strength of catgut in the tissues of dogs as compared with that observed in patients (series 1937; company 3).

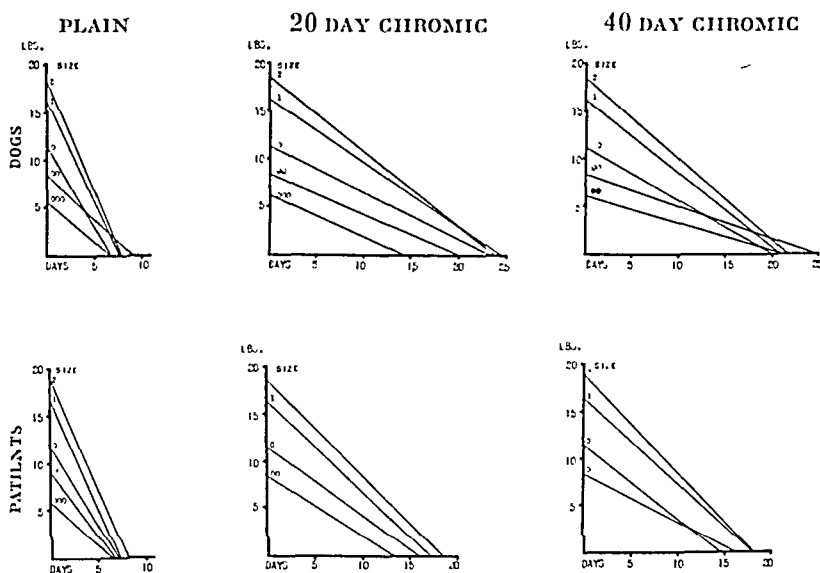


Fig. 10.—Graphs showing decline in tensile strength of catgut in the tissues of dogs as compared with that observed in patients (series 1937; company 4).

The various brands of twenty day or forty day chromic or tanned catgut can be classified only in a general way into three categories: (1) those which did not maintain their tensile strength for a period of ten days; (2) those which held up for ten to fifteen days; (3) those which kept their tensile strength for fifteen to thirty days.

It was frequently difficult to classify a particular type of chromic catgut (i. e., twenty day or forty day) of any one company within the bounds of one of these rather broad categories if the various sizes were taken into consideration. There were numerous instances in which certain sizes performed within the range of one category while other sizes were sufficiently different in behavior to be within the bounds of another category. In fact, some products showed such variation that it was necessary to classify that particular type of catgut in all three categories, depending on the particular size of the catgut.

This phenomenon of difference in behavior of various sizes of chromic catgut of the same company was a rather conspicuous observation in this work. It was frequently observed that the smaller sizes of chromic catgut outlasted the larger sizes from the standpoint of duration of tensile strength. In some products, however, the larger sizes held up better than the smaller. In occasional instances, the duration of tensile strength of different sizes was rather inconsistent, so that no general trend of behavior could be ascertained. It was rather unusual to find a chromic catgut product which had a fairly uniform duration of tensile strength in both large and small sizes. As far as any one product was concerned, the general trend of behavior as related to size was fairly consistent in both the twenty day and the forty day type of catgut.

The graphs showing decline in tensile strength of catgut in the tissues of the dog as compared to the tissues of the patient (fig. 4) were to a considerable extent comparable. In general, the plain catgut was inclined to last about a day longer in patients than in dogs, although the chromic catgut showed a tendency to hold up a few days less in patients than in the animals.

Regarding the individual tests conducted on any particular size, type or brand of catgut, there was a considerable amount of variation in the observations made. This was true to some extent even of duplicate implants from the same strand used in two different animals. A comparison of different sizes, types or brands of catgut could reasonably be made only on the basis of an average of individual tests. At least six to twelve individual results were usually considered in the average which was plotted on the graphs. It should not be overlooked that this average represents an approximate range of behavior rather than a precise evaluation of the duration of tensile strength of any particular catgut.

The calculated end points based on the various individual observations on any particular catgut were usually dispersed in such a way that a considerable proportion of them were within a narrower bracket than

the range between the maximum and the minimum duration of tensile strength. For example, let a catgut which ordinarily averages ten days' duration of tensile strength be considered. The earliest loss of tensile strength in the various tests might be calculated at six days, while the longest duration for this particular catgut might be fourteen days. The maximum-minimum range of variation is therefore eight days. It was usually found that the bulk of the observations indicated a duration of tensile strength between eight and twelve days, which is a bracket of one half of the maximum-minimum range. For catgut which was within the fifteen to thirty day category, the maximum-minimum range was somewhat greater than that observed for the ten to fifteen day classification.

COMMENT

The rather striking differences in the results obtained with different brands of catgut suggest the need for an improvement in the criterion used by various manufacturers for determining the manner, the method or the extent of treatment, such as chromicizing or tanning, which is used in the preparation of surgical sutures. Further, it appears that the terms used to designate different types of chromic or tanned catgut, such as twenty or forty day, were to a considerable extent misnomers as far as duration of tensile strength in the tissues was concerned. There is little doubt but what the Committee of Revision of the United States Pharmacopeia has taken a justifiable step in the elimination of such terms from the labels of catgut.

Although it has been customary for most general surgeons to use a so-called twenty day chromic catgut for suturing the fascia, especially in abdominal incisions, it appears from these tests that only a minority of surgeons actually used catgut which maintained its tensile strength for a period anywhere near twenty days. An important aspect to consider is what duration of tensile strength has been found by the practical use of catgut to be most desirable for closure of the fascia in the ordinary run of cases of the average general surgeon. Judging from the various products tested, there must be some rather definite reason why the larger sizes of chromic catgut of so many companies do not hold up much beyond ten days. A point to be considered is that if the larger sizes of catgut are chromicized enough to maintain tensile strength for fifteen to twenty days, it is probable that difficulties may arise from this kind of catgut because of the delayed absorption of large bulky knots which may occasionally cause a draining sinus which does not heal until the catgut knot is absorbed or extruded.

The problem of ultimate complete absorption of catgut will be fully discussed in a subsequent paper. It will suffice to say at this time that the complete absorption of chromic catgut after it loses its useful holding power in the tissues is a matter of months if the duration of tensile

strength is beyond ten days. It is believed that the main reason that so much of the chromic catgut in the larger sizes does not hold up beyond ten days is that the manufacturers have found from experience that the tissues do not well tolerate a more thorough chromicizing if so much bulk of suture material is concerned. If a draining sinus develops in a case in which this type of material is used, the surgeon will complain about the catgut. If the manufacturer receives a number of complaints, there is little choice but to make the larger sizes of chromic catgut less resistant to absorption. For the larger sizes of chromic catgut, it is therefore probable that a duration of tensile strength of ten days is about as much as can be expected, in view of the relatively satisfactory clinical results obtained with products which seldom hold up as long as ten days by the tests described. On the other hand, it is possible that improvements in methods of chromicizing may permit a somewhat more resistant suture to be used in the larger sizes without causing an appreciable amount of trouble from draining sinuses in the wounds.

In the smaller sizes, a more thorough chromicizing may be given without causing practical difficulties in the way of draining sinuses, because the lesser bulk of suture material is apparently much better tolerated by the tissues. It is probably because of this that the smaller sizes of chromic catgut of a considerable number of companies showed up better in the tests than the larger sizes. It appears that these companies are attempting to graduate their chromicizing to the relative graded tolerance of the tissues to different sizes of suture material.

It is difficult to understand why there should be appreciable differences in the behavior of various brands of plain catgut and also why a brand of plain catgut might outlast another brand of so-called twenty day or forty day chromic or tanned catgut. There are several sources of supply of the raw catgut available to suture manufacturers. In some instances, the suture manufacturer controls the source of supply. There are probably various methods used in the preparation of the raw product from sheep intestines. If there are appreciable differences in the method of preparation of the raw product before it becomes available to the suture manufacturer, it is not inconceivable that the raw product from one source might differ from that obtained at another source with regard to inherent resistance to absorption. When plain catgut is prepared for surgical use, it is probable that differences in the behavior of different brands of this type of catgut may be due to differences in the methods employed in preparing the raw product.

Further, it is possible that some chromicizing methods may not adequately increase the resistance to absorption of relatively poorly resistant raw catgut to make this outlast plain catgut from another source in which the raw catgut may already possess considerable resistance without additional treatment, such as chromicizing or tanning. Another

factor which may enter into this situation is that the method of preparation of the raw catgut may impart to it certain qualities which in some way tend to negate the effective action of the chromicizing process designed to increase the resistance of the catgut strand to tissue absorption.

The various manufacturers of surgical sutures carry out with considerable precision methods of chromicizing which are designed to render their product as uniform as possible in its behavior in the tissues. Nevertheless, different lots of the finished products sometimes appear to be lacking in uniformity of absorption. This lack of uniformity may be of a magnitude which is appreciably greater than the range of variation of any particular catgut in different test animals. One cannot help but feel that attempts to improve the present variability of catgut behavior in the tissues should be directed at least to some extent toward a more uniform control of the conditions under which the raw produce is prepared.

To the question of whether these tests conducted in dogs are reliable in ascertaining the behavior of catgut in human tissues, the rather striking similarity in the decline in tensile strength shown in the charts (fig. 4) should be an adequate answer. Further, the results of these tests in dogs were to a considerable extent comparable to the observations made by Wolff and Priestley⁴ on the duration of tensile strength of catgut in patients. They also observed that some brands of plain catgut outlasted other brands of so-called twenty day chromic catgut. In addition, they drew attention to the greater degree of resistance to absorption of smaller sizes of chromic catgut of some products.

It is probable that the slightly longer duration of tensile strength of the plain catgut in patients as compared to the duration in dogs was due to the fact that some tension was maintained throughout the clinical tests. This delayed the rate of disintegration of the plain catgut, which usually tends to unravel rather conspicuously at the plies when it is placed in tissues without some tension, as was done in the dogs. When catgut unravels freely in the tissues, the phagocytic cells have an opportunity to attack a much greater surface area, and hence the absorption might be expected to be accelerated. The slightly shorter duration of tensile strength of the more resistant type of chromic catgut in patients is probably due to the method of implantation in patients. There may be some reaction in the skin around the catgut at the points at which the catgut comes out through the skin when the tests are carried out longer than ten days. This amount of reaction could cause a slightly more rapid decline in tensile strength of the catgut in the patients. It was rather interesting to observe that the catgut which held up approximately ten days in the patients maintained also its tensile strength in dogs for the same length of time.

SUMMARY

The decline in tensile strength of plain and chromic or tanned catgut of various sizes produced by different manufacturers has been studied by a series of 1,500 catgut implants in the abdominal muscles of dogs. This survey has included the products of ten companies, some of which have been checked over a period of three or four years.

The rate of decline in tensile strength of catgut in the abdominal muscles of dogs under the conditions prevailing in the tests was reasonably comparable to that observed in the laparotomy wounds of patients when tested by a method previously described as the tension suture test.

Plain catgut was usually found to undergo complete loss of tensile strength within about five or six days, although in some instances the duration of tensile strength was appreciably longer, even extending beyond ten days.

The duration of tensile strength of the various sizes of twenty day and forty day chromic catgut (now labeled type C, medium chromic, and type D, extra chromic, respectively) of the various manufacturers was classified rather broadly into three categories: less than ten days; ten to fifteen days; fifteen to thirty days.

There was a rather noticeable difference in the behavior of the products of the various manufacturers, although only slight differences were observed in comparisons of the twenty day chromic with the forty day chromic catgut of any one company.

The size of the chromic catgut was usually conspicuously related to its behavior in the tissues. In certain products, the smaller sizes outlasted the larger sizes, although in other products the larger sizes held up longer than the smaller sizes. In occasional instances, however, the size of the catgut was not related to any general trend of behavior in the tissues.

CONCLUSIONS

The implantation technic described offers a satisfactory direct method of evaluating the absorption qualities of surgical gut (catgut) from the standpoint of the rate of decline of its tensile strength in the tissues.

The nomenclature formerly used by many manufacturers to designate the absorption time of their products, such as twenty day and forty day chromic catgut, was sufficiently unrelated to the duration of tensile strength of most products so designated that the discontinuation of this nomenclature is in the best interests of the surgeon as well as of the manufacturer.

It is probable that a duration of tensile strength of about ten to fifteen days may be better suited to the needs of the average general surgeon for routine closure of fascial layers, especially when large sizes of chromic suture material are used.

ACUTE APPENDICITIS

A CLINICAL AND PATHOLOGIC STUDY OF 1,680 CONSECUTIVE CASES

JOHN E. JENNINGS, M.D.

HERBERT H. BURGER, M.D.

AND

MENDEL JACOBI, M.D.

BROOKLYN

This paper is a study of 1,680 consecutive unselected cases of acute appendicitis which occurred at the Beth-El Hospital between the years 1930 and 1938, inclusive. The report is based only on cases in which there was pathologic evidence that warranted classification of the condition as acute. No case in which the condition was not diagnosed pathologically as acute is included, regardless of the clinical diagnosis. Parenthetically, it may be noted that during the period under survey there were 194 cases, or 11.6 per cent of the 1,680, in which the patients were admitted with a diagnosis of acute appendicitis which pathologic examination including microscopy failed to confirm.

In evaluating our figures, a brief description of the service is important. The hospital, of some 280 beds, is situated in one of the most congested and densely populated districts in the city of New York (population about 350,000 in about 3 square miles [777 hectares]). This hospital served until recent years almost exclusively the lower middle class or poor patient in this district in the capacity of a voluntary hospital. The average income of a family among its patients was about \$1,300 per year; many were on the rolls of various governmental relief agencies. With few exceptions, however, the patients were all literate and frequently were well educated. They were preponderantly Jewish; there were but an occasional Negro and a moderate sprinkling of Italian or Irish patients in this series.

In 59 per cent of the cases here analyzed, the patients were treated as private or semiprivate patients of the various members of the inpatient surgical staff, while in 41 per cent, the patients were treated as ward or free patients by the surgical staff then on service.

It should be stated that the surgical staff and the facilities of the hospital have been substantially the same throughout the period under consideration. It is of importance that all members of the surgical staff beneath the grade of attending surgeon (two men) or associate attend-

From the Departments of Surgery and Pathology, Beth-El Hospital.

ing surgeon (two men) were supervised in all cases, both before and after operation and during any surgical procedures, by an attending or an associate attending surgeon, regardless of whether the patient was considered a ward, a free or a private patient. All appendixes removed were routinely subjected to careful gross and microscopic examination; in each instance, regardless of the gross findings, sections from the distal, middle and proximal thirds and from the tip beyond the gross lumen were examined. In special cases, additional sections from points of special gross interest were taken.

One further fact is of importance. The people of the district served by the hospital, though in poor financial circumstances as noted before, have, in general, been subjected to a high degree of education by various social and medical groups concerning the dangers of the so-called

TABLE 1.—*Relation Between Preoperative Duration of Symptoms and Mortality Rate*

Duration of Symptoms	Patients	Percentage of Total	Deaths	Percentage
6 hours.	71	4.1	0	0
12 hours	315	18.8	1	0.31
24 hours	588	35.03	8	1.3
48 hours	326	19.4	7	2.1
3 days..	152	9.09	5	3.28
4 days.	86	4.4	2	2.38
7 days.	91	4.7	1	7.86
2 weeks	33	1.9	2	6.06
3 weeks	6	0.3	0	0
4 weeks .	4	0.22	0	0
Over 6 weeks	8	0.46	0	0

bellyache. Physicians, 88 per cent of whom were trained in American or English schools, are easily accessible (416 physicians for 350,000 people) and are likely to be called fairly early to see the patient (table 1 shows that 971 of this series, well over half, were operated on within twenty-four hours of the first symptom, and 1,296, within the first forty-eight hours). Finally, the hospital conducts an active ambulance service of three ambulances, averaging fifty calls per day, and the ambulance surgeons are instructed to hospitalize all patients if there is a suggestion of appendicitis and to prescribe or administer no narcotics or laxatives to patients whose symptoms in any way suggest the presence of an acute condition within the abdomen.

GENERAL INCIDENCE

During the last eight years, there were 1,680 cases of acute appendicitis substantiated by histologic survey. There were 32 deaths; this represents a total uncorrected mortality rate of 1.9 per cent. In all but

8 cases in this series, operation was done. Pathologic reports of the underlying condition ranged from acute catarrhal to acute gangrenous appendicitis with rupture and generalized peritonitis.

SEX AND AGE INCIDENCE

In 909 of our cases, the patients were male, and in 771, they were female. Since our general hospital population is about 1.2 male patients to 1 female, it can readily be seen that acute appendicitis is more prone to occur in the male. This is particularly true in children under the age of 12. A study of age incidence shows that the second and the third

TABLE 2.—*Incidence of Acute Appendicitis with Regard to Age, Sex, Signs, Symptoms, Morbidity, Complications and Death*

Age Group, Years	Patients	Sex		Signs, Symptoms and Laboratory Data										
		Male	Female	Abdominal Cramps, With or Without Localization in the Right Lower Quadrant	Nausea	Vomiting	Temperature (100 F. or Higher)	Leukocytosis, With or Without Polynucleosis	Diarrhea, Two or More Watery Stools	Chills	Frequency of Urination and Dysuria	Backache	Morbidity and Complications	Deaths
1-10	332	195	137	301	275	234	270	268	0	1	5	12	56	12
11-20	613	332	281	604	560	416	491	510	7	6	5	2	55	4
21-30	398	205	193	434	331	228	292	313	2	9	6	1	26	6
31-40	169	97	72	160	130	80	127	135	2	6	6	1	17	4
41-50	88	44	45	73	63	40	61	60	0	6	7	0	5	3
51-60	43	28	15	40	38	29	36	40	0	2	1	0	6	1
61-70	14	8	6	13	11	6	11	11	0	0	0	0	4	2
Over 71	3	1	2	2	2	2	2	0	0	0	0	0	0	0
Total	1,680	909	771	1,627	1,410	1,035	1,290	1,347	11	30	30	6	169	32
				97%	84%	61%	77%	79%	0.7%	1.7%	1.7%	3.4%	10%	1.9%

decades of life and particularly about the age of 18 in both sexes is the time that the disease most frequently occurs. The youngest patient in our series was 17 months old and the oldest 81 years (table 2). This age distribution corresponds roughly with that of the population of the district.

CAUSATION

The causative factor in the production of acute appendicitis is still far from being conclusively established.¹ The most generally accepted theory on an anatomic and a physiologic basis is the one which postu-

1. (a) Bowers, W. F.: Appendicitis, with Special Reference to Pathogenesis, Bacteriology and Healing, Arch. Surg. 39:362 (Sept.) 1939. (b) Krecke, A.: Ueber die Ursachen und das Wesen des Appendizitis, Munchen. med. Wchnschr 80:299, 1933.

lates a constant surge of fecal material high in bacterial content, passing through a long thin organ rich in susceptible lymphoid tissue, in which stasis may occur to a greater or a lesser degree with resultant inflammatory process. This stasis may be aided by mechanical block of fecaliths,² foreign bodies or kinks; with interference in the emptying of the appendix, distention results and decreases the resistance of the mucosa and renders this easy prey for the massive amount of organisms already present. It should be noted, however, that in only a small percentage of the cases (14) of our series were there evidences of obstruction by fecaliths, stenosis or external constricting agents; this is in contrast with the high incidence of these conditions found by Wangensteen^{2b} and Bowers^{1a} and others.³ In this regard, our findings parallel those of the recent study by Koster and Shapiro⁴ as well as the older figures given by Aschoff⁵ and Burgess.⁶

In our series, 65 patients, or 3.8 per cent of the entire series, gave a history of preceding infection of the upper part of the respiratory tract. Acute appendicitis may occur by way of the blood stream from the respiratory tract,⁷ and when it does occur in this way, it is of a more fulminating character, the process going on to gangrene within a short time. All our patients with an antecedent history of infection of the respiratory tract showed gangrenous appendicitis at operation. All 65 were operated on within forty-eight hours of onset of abdominal symptoms. The antecedent history of infection of the respiratory tract varied from two to six days before the onset of abdominal symptoms. No emboli could be demonstrated in any appendix in this group, nor was there any evidence of obstruction of the organ due to swollen lymphadenoid tissue, as suggested by Bowers,^{1a} or of any other obstructive agent. The lymphoid changes in these appendixes were, in common

2. (a) Aschoff, L.: Ueber die Bedeutung des Kotsteines in der Aetiologie der Epityphlitis, *Med. Klin.* **24**:587, 1905. (b) Wangensteen, O. H., and Bowers, W. F.: Significance of the Obstructive Factor in the Genesis of Acute Appendicitis, *Arch. Surg.* **34**:496 (March) 1937.

3. Van Zwalenburg, C.: Relation of Mechanical Distention to the Etiology of Appendicitis, *Anp. Surg.* **41**:437, 1905. Wilkie, D. P. D.: Acute Appendicitis and Acute Appendicular Obstruction, *Brit. M. J.* **2**:959, 1914.

4. Koster, H., and Shapiro, A.: Role of Intraluminal Obstruction in Pathogenesis of Acute Appendicitis, *Arch. Surg.* **41**:1251 (Nov.) 1940.

5. Aschoff, L.: *Die Wurmfortsatzentzündung*, Jena, Gustav Fischer, 1908; footnote 2a.

6. Burgess, A. H.: A Clinical Lecture on an Analysis of Five Hundred Consecutive Operations for Acute Appendicitis, *Brit. M. J.* **1**:415, 1912.

7. Adrian, C.: Die Appendicitis als Folge einer Allgemeinerkrankung. *Klinisches und Experimentelles*, *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* **7**:407, 1901. Anderson, H. B.: Appendicitis as a Sequel of Tonsillitis, *Am. J. M. Sc.* **150**:541, 1915. Equen, M.: Appendicitis Following Tonsillectomy: A Clinical Study, *Tr. Sect. Laryng., Otol. & Rhin., A. M. A.*, 1932, p. 130.

with those seen in children generally or in adults in whom the lymphoid follicles were still largely extant, confined to moderate proliferation of the reticulum cells of the secondary follicles, moderate enlargement of these follicles at the expense of the follicle as a whole and the adjacent lymphoid stroma and the presence, in the more severely involved organs, of focal nonspecific necrosis in the secondary follicles, in all respects similar to those seen in secondary lymphoid follicles affected by a variety of generalized infections and exanthems. Careful review of these 65 specimens failed to reveal any occlusion or stenosis or measurable distention of the lumen in any portion of the organ.

Trauma seems to have been the causative factor in 6 cases, or 0.34 per cent of our series. Five of these patients were thin wiry persons belonging to age groups below 20 years.

Fibrocascous tuberculosis of the appendix with a superimposed acute phlegmonous process was found to be the causative factor in a woman of 33 years, with a typical history of twelve hours' duration of symptoms. The lumen was stenosed proximally by the fibrosing phase of tuberculosis.

Though carcinoid was encountered in 8 cases of this series, the tumor gave no evidence of obstruction pathologically and did not appear clinically to have had any bearing on the development of acute infection. In every instance the neoplasm was an incidental finding.

Our classification of acute appendicitis, as are all morphologic classifications of disease processes essentially dynamic and changing, is admittedly arbitrary. It is of value only as indicating the degree to which the process had advanced when the organ was removed. We believe that by the use of the method of examination of the appendix previously described in brief, a rather comprehensive picture of the process in all parts is obtained. Comparison of the information obtained from these sections with that obtained from longitudinal sections⁸ has not convinced us that the latter, somewhat more difficult technically and certainly delaying histologic study (since the organ must first be fixed in toto), yields more exact details. In fact, we have found study of the appendical mural lymphatics and vessels more complete when sections of the entire wall at right angles to the long axis were examined. Further, this method allows the surgeon to be informed of complete pathologic details within twenty-four hours after receipt of the appendix by the laboratory and to guide his further treatment of the case aided by such study. An added objection to longitudinal sectioning is that the necessary preliminary fixation of the organ in toto effectively prevents study of the interior and the wall of the appendix in the natural state.

8. Bowers.^{1a} Wangensteen and Bowers.^{2b}

Our department of pathology has throughout the last twelve years looked with considerable disfavor on the pathologic diagnosis of acute catarrhal appendicitis, realizing that at least two of the criteria so often relied on for such a diagnosis—congested vessels and so-called stromal edema—can easily be simulated by the effects of suddenly clamping or ligating the mesoappendix early in the operation or even by mere mechanical handling at the operating table. To make such a pathologic diagnosis, this department has therefore insisted on the presence histologically and in an obvious fully developed manner of all of the following findings:

1. Marked congestion of the mucosal stromal capillaries must be present with a greater proportion of polymorphonuclear leukocytes in the intraluminal blood than in normal circulating blood, i.e., more than 1 to about 500.

2. These leukocytes must be arranged chiefly at the periphery of the vessel, i.e., show the phenomenon of so-called margination, preferably with some evident emigration through the wall.

3. There must be widespread and more or less uniform marked stromal edema.

4. There must be such a marked increase in the polymorphonuclear leukocytes in the stroma—exclusive of eosinophils, which are ordinarily seen in rather large numbers in the mucosal stroma of a noninflamed appendix, especially as a postcibal finding—as to be easily evident under the low power objective of a microscope. Such leukocytes must be rather uniformly distributed.

5. The mucosal glands must be so distended with mucoid secretion that the lining cells show evidence of compression.

With these criteria, there have been only 57 cases in this series (.03 per cent) in which the diagnosis of acute catarrhal appendicitis has been made. Determination of the number of cases of this condition is important in any statistical study since the appendix in this condition is, by definition, more mildly involved. It should be noted that even in these cases there was the added corroborative evidence of inflammation in the presence of distended leukocyte-filled mural lymphatics, vessels not ordinarily seen at all or recognized only doubtfully in the normal organ. This we have chosen to regard as evidence of regional drainage in the same sense as regional lymphangitic drainage in any other infected organ and have termed it appendical lymphangitis. Its significance in appendical inflammation will be discussed in a later communication as well as briefly considered in this paper. In a few instances, chiefly in association with more severe grades of inflammation, we have even seen the lymphangitic process involving mesoappendical vessels.

By acute phlegmonous appendicitis we have designated that picture in which all the layers of the appendix to greater or lesser degree and in widespread or focal manner show evidence of extravascular leukocytic infiltration, with other evidences of inflammation as noted. There is, however, either no or little necrosis of tissue; the mucosa is not ulcerated, and there is no intraluminal purulent exudate, though there may be and frequently is a peritonitic reaction. When mucosal ulceration and pus in the lumen of the appendix (microscopic or grossly frank pus, not tissue juices grossly mistaken for pus) are present, appendicitis is classified as acute suppurative. The term acute gangrenous appendicitis is reserved for organs which show, in the involved portions, a predominance of necrosis of tissue with consequent obliteration of the usual landmarks; perforation need not be present.

We have further included, as a subsection of these classes, the presence of gross fibrosis sufficient to obliterate the lumen. This finding, wherever noted, required microscopic confirmation. Finally, we have noted also the presence of marked leukocytic infiltration of the walls of arteries or veins, with or without thrombosis, as acute arteritis or phlebitis, and the presence of the lymphangitic mural and mesoappendical involvement as given under the description of the catarrhal appendix. These findings were noted in an attempt to obtain information as to whether their presence affects the prognosis or the morbidity in a case.

The finding of localized peritonitis, with or without the formation of abscess, or generalized peritonitis was strictly a gross observation at operation.

RELATION OF APPENDICITIS TO MORBIDITY AND MORTALITY RATES

Table 3 shows, as was to be expected, no morbidity or mortality associated with the catarrhal appendix. So strikingly uniform are these figures that we were willing, despite our rather severe pathologic criteria, to consider the appendix as not the cause of the clinical syndrome except for the fact that a follow-up study of these comparatively few cases revealed no recurrence of similar symptoms up to two to four years after operation.

When frank suppurative, phlegmonous or gangrenous inflammation occurred, both the morbidity (11.2 per cent) and mortality rates (2.2 per cent) were highest. The added finding of appendical lymphangitis was associated with a rather marked drop in the morbidity (5.9 per cent) and the mortality rate (1.05 per cent). Similarly, the presence of arteritis or phlebitis in association with suppurative or gangrenous disease was again associated with considerable reduction in the morbidity (7.1 per cent) and mortality rates (1.6 per cent) as compared

with the simple suppurative-gangrenous series, though the presence of arteritis or phlebitis is associated with about 1.2 times as great a morbidity rate and 1.6 times as great a mortality rate as the suppurative-gangrenous type showing a lymphangitic picture alone as a pathologic concomitant. These figures suggest that lymphangitis acts as a defense mechanism to prevent the spread of appendical infection and that arteriophlebitis acts in a similar, though less efficient, manner. That lymphangitis may have such a function was experimentally suggested by Menkin⁹ and Lurie,¹⁰ who like ourselves, found it not absolute.

TABLE 3.—*Relation of Appendicitis to Morbidity and Mortality Rates*

Age Group, Yr.	Acute Catarrhal Appendicitis			Acute Suppurative Gangrenous Appendicitis			Acute Suppurative Gangrenous Appendicitis plus Lymphangitis			Acute Suppurative Gangrenous Appendicitis plus Lymphangitis and Arteriophlebitis		
	Cases	Morbidity	Mortality	Cases	Morbidity	Mortality	Cases	Morbidity	Mortality	Cases	Morbidity	Mortality
1-10	14	0	0	235	42	8 3.4%	54	9	2 3.6%	37	7	2 5.4%
11-20	25	0	0	406	44	3 0.7%	109	2	1 0.9%	72	3	0
21-30	11	0	0	286	21	5 1.7%	72	2	0	37	1	1 2.7%
31-40	4	0	0	118	10	4 3.4%	38	4	0	18	1	0
41-50	3	0	0	67	3	3 4.4%	10	0	0	7	0	0
51-60	0	0	0	32	6	1 3.1%	2	0	0	7	0	0
61-70	0	0	0	14	4	2 15%	0	0	0	0	0	0
Over 70	0	0	0	2	0	0	0	0	0	0	0	0
Total	57	0	0	1,160	130	26 11.2% 2.2%	285	17	3 5.9% 1.05%	178	12	3 7.1% 1.6%

RELATION OF DURATION OF ILLNESS TO MORTALITY

The question of length of illness from the onset of the first symptom and its subsequent effect can be seen in table 1. It will be noted that the death per hundred cases of acute appendicitis is definitely increased with a history of forty-eight hours or longer (40.4 per cent of all cases in this series).

9. Menkin, V.: An Aspect of Inflammation in Relation to Immunity, Arch. Path. **12**:802 (Nov.) 1931; Studies on Inflammation: V. The Mechanism of Fixation by the Inflammatory Reaction, J. Exper. Med. **53**:171, 1931; Dynamics of Inflammation, New York, The Macmillan Company, 1940, pp. 115, 152, 169 et seq., 183 et seq. and 200 et seq.

10. Lurie, M. B.: Role of Extracellular Factors and Local Immunity in the Fixation and Inhibition of Growth of Tubercle Bacilli, J. Exper. Med. **69**:555, 1939.

The absence of death in cases of over three weeks' duration is not significant, there being too few cases (18 in all) in this group. Of these, 6 were cases of walled-off abscess. Ten patients in this group noted their first symptoms suggesting acute appendicitis three weeks or longer before operation, but the symptoms thereafter were of such a character as to suggest recurrent attacks rather than that the inflammation of the organ was continuous from the date of the first symptom. It was, however, practically impossible to assign such cases to a more exact temporal relation than that noted in the table.

SIGNS, SYMPTOMS AND LABORATORY DATA

In our cases the signs, symptoms and laboratory data agree with similar details so frequently commented on by other authors. The five cardinal signs and symptoms of Murphy were, in our series, by far the most prominent. Whenever laboratory data did not confirm well marked clinical findings, the former were discounted, usually correctly. We have not found that the Arneth or Schilling counts yielded sufficient additional information as compared with the usual differential count to warrant using these more time-consuming and operation-delaying procedures. Variations in the clinical picture have, in our experience, occurred chiefly in the youngest and oldest groups, in both of which greater reliance has been placed on physical findings (including rectal examination) than on symptoms. Of the latter, nausea and vomiting tended to approximate pain in point of frequency of occurrence. The statistical incidence of signs and symptoms is presented in table 2.

Catharsis definitely plays a part in the progress of the underlying pathologic process. Purging was present in the history in an overwhelming majority of cases that had gone on to gangrenous appendicitis with peritonitis. Twenty-eight (87.5 per cent) of the patients who died gave a history of catharsis.

An attempt was made to correlate the pathologic picture found at operation with the signs and symptoms. It was found, however, that, with the exception of the fact that in every one of the 30 cases in which there were chills there was histologic arteritis or phlebitis or both, no such correlation could be made. Parenthetically, it may be noted that in this series chills were not of grave prognostic import as has been suggested by others.¹¹ Of the 32 patients who died, only 4 gave a history of chills. The other 26 patients giving a history of chills made an uneventful recovery not delayed or complicated in any manner as

11. Royster, H. H.: *Appendicitis*, New York, D. Appleton and Company, 1927, p. 114. Colp, R.: *Thrombophlebitis of Appendicular Origin*, *S. Clin. North America* 19:443, 1939. Thalheimer, W.: *Chills Occurring Early in Appendicitis Before Operation and Their Indication of Operable Stage of Pylephlebitis*, *Arch. Surg.* 8:658 (March) 1924.

compared with the recovery of the patients without chills. Our findings agree with those of Strauss and Tomarkin.¹²

Similarly, there was no possible correlation in the suppurative-gangrenous series, between the character of the pathologic changes and the duration of symptoms. In fact, even perforation was found, in

TABLE 4.—*Postoperative Complications of Acute Appendicitis*

Complication	Cases
Peritonitis	41
Generalized (perforation in 27 cases) (at operation).....	33
Localized (perforation in 6 cases) (at operation).....	8
Respiratory disease	32
Pneumonia	18
Infection of the upper part of the respiratory tract (postoperative).....	8
Collapse of the lung.....	3
Pulmonary embolus	3
Residual abscess (postoperative).....	25
Pelvic	22
Interintestinal	1
Subphrenic	2
Wound infection	12
Intestinal obstruction	9
Acute mechanical (preoperative).....	5
Paralytic adynamic ileus (postoperative).....	4
Acute cardiovascular collapse.....	4
Pyelonephritis (preoperative)	4
Diabetes mellitus	4
Thrombophlebitis (postoperative, all in the left leg).....	3
Evisceration	3
Operative fistula	3
Suppurative pyelophlebitis (postoperative).....	2
Rheumatic fever	2
Otitis media (preoperative).....	2
Scarlet fever (preoperative).....	2
Infectious arthritis (preoperative).....	2
Aseptic meningitis (probably due to spinal meningitis).....	2
Salpingitis (preoperative concomitant).....	2
Abdominal cellulitis (postoperative).....	1
Subcutaneous hematoma (postoperative).....	1
Coronary thrombosis (postoperative).....	1
Nondiabetic acidosis (postoperative).....	1
Pregnancy	1
Acute gastric dilatation (postoperative).....	1
Chickenpox (preoperative)	1
Fibromyoma uteri	1
Epigastric hernia (preoperative).....	1
Chronic cystic mastitis.....	1
Hemolytic icterus (preoperative).....	1
Ureteral calculus (preoperative).....	1

association with a relatively short history of six hours' or less duration of symptoms (72 cases). These facts again emphasize the dangers of delaying operative intervention in the hope of subsidence, except for reasons hereinafter noted.

12. Strauss, A., and Tomarkin, S.: *Acute Appendicitis, Surgery* 3:111, 1938.

POSTOPERATIVE COMPLICATIONS

There were complications or accompanying conditions in 166 cases (9.9 per cent) of our entire series. Complications occurred much more frequently in the younger and older age groups. These cases are classified in table 4.

MORTALITY

The total mortality rate of the series was 32 of 1,680 patients, or 1.9 per cent (table 3), as compared with a death rate for all cases in the district of 1.1 per cent. Of these, 21 patients were male, and 11 were female. It is interesting to note at this time that not only is acute appendicitis more common in males but that it assumes in them a more

TABLE 5.—*Causes of the Thirty-Two Deaths in the Present Series of 1,680 Cases of Acute Appendicitis*

Cause of Death	Cases
Generalized peritonitis	15.
Perforated	11
Nonperforated	4
Intestinal obstruction	3
Perforated appendix	0
Nonperforated appendix	3
Peripheral circulatory collapse.....	2
Bronchopneumonia	2
Pulmonary embolus	2
Diabetic coma	2
Generalized toxemia, nonperitonitic.....	2
Coronary thrombosis	1
Suppurative pyelophlebitis	1
Evisceration	1
Acute gastric dilatation.....	1

lethal character. Reference to tables 2 and 3 shows that the greatest number of deaths occurred at the extremes of life; this probably was due to the fact that in these cases the condition was less typical, purging was resorted to more often, and consultation with the physician was late. It is also apparent that dangers increase geometrically in cases in which there is a history of over forty-eight hours' duration of the condition and in which the appendix has perforated without localization. In 60 per cent of the cases in which death occurred, or 19, there was a history of duration of forty-eight hours or longer. In each of these there was an advanced process in the appendix with or without perforation. Table 5 summarizes the causes of death.

Table 6 is a summary of the mortality percentage of other large series of cases reported in the literature. Our figure of 1.9 per cent is not altered, even by excluding the cases of acute catarrhal appendicitis as possible errors of diagnosis. Similar correction of other published

studies containing large numbers of catarrhal appendixes substantially raises the recorded mortality rate.

Early in this study we were impressed by the relative frequency with which death of patients operated on at night occurred.¹³ Study of the cases of our 32 dead patients showed that 21 (66 per cent) were operated on at night (after 9 p. m.) or in the early morning hours.

TABLE 6.—*Summary of Mortality Rates in Large Series of Cases of Acute Appendicitis Published Since 1931*

Author	Cases	Mortality Rate, per Cent
Tasche, L. W., and Spano, J. P.: <i>Ann. Surg.</i> 94 : 899, 1931.....	700	3.40
Hjelmman, G.: <i>Acta Soc. med. fenn. duodecim</i> (Ser. B, fasc. 1, art. 2) 17 : 1, 1932; abstracted, <i>J. de chir.</i> 42 : 465, 1933.....	5,287	2.67
Keyes, E. L.: <i>Ann. Surg.</i> 99 : 47, 1934.....	1,859	3.35
Seifert, E.: <i>Deutsche Ztschr. f. Chir.</i> 244 : 176, 1934.....	1,350	6.80
Donaldson, H. H.: <i>Pennsylvania M. J.</i> 38 : 73, 1934.....	2,700	4.80
Quain, E. P.: <i>Arch. Surg.</i> 28 : 782 (April) 1934.....	2,000	3.25
Weyill, L. B., and Wallace, H. L.: <i>Edinburgh M. J.</i> 41 : 557, 1934.....	8,265	4.40
Stanton, E. M.: <i>Surg., Gynec. & Obst.</i> 59 : 738, 1934.....	16,424	5.40
Müller, S.: <i>Hospitaltid.</i> (no. 30) 77 : 34, 1934.....	1,087	6.00
Cayford, E. H.: <i>Canad. M. A. J.</i> 32 : 259, 1935.....	614	3.40
Krech, S.: <i>New York State J. Med.</i> 35 : 248, 1935.....	4,662	7.00
Ramsdell, E. G.: <i>New York State J. Med.</i> 35 : 673, 1935.....	1,013	2.40
McKenna, H.: <i>Ann. Surg.</i> 104 : 617, 1936.....	1,257	5.00
Schullinger, R. N.: <i>Arch. Surg.</i> 32 : 65 (Jan.) 1936.....	2,653	5.08
Jensenius, H.: <i>Ugesk. f. læger</i> 98 : 1085, 1936.....	1,592	6.85
Loveland, J. E.: <i>Am. J. Surg.</i> 31 : 87, 1936.....	1,275	2.80
Rhodes, G. K.; Birnbaum, W., and Brown, M. J.: <i>California & West. Med.</i> 45 : 458, 1936.....	1,000	3.60
Leonard, E. D., and Derow, S.: <i>New England J. Med.</i> 214 : 52, 1936.....	1,000	6.40
Reid, M. R.; Poer, D. H., and Merrell, P.: <i>J. A. M. A.</i> 106 : 665 (Feb. 29) 1936.....	2,806	6.40
Burghardt, M.: <i>M. Times & Long Island M. J.</i> 64 : 181, 1936.....	892	3.90
Young, J. R.: <i>South. Surgeon</i> 6 : 131, 1937.....	1,734	4.3
Lazzarini, L.: <i>Riforma med.</i> 53 : 123, 1937.....	800	12.0
Sperling, L., and Myrick, J. C.: <i>Surgery</i> 1 : 255, 1937.....	518	5.6
Davis, J. E.; Muske, P. H.; Mulligan, P. L., and Gutov, J.: <i>J. A. M. A.</i> 108 : 1498 (May 1) 1937.....	10,000	3.8
Holder, H. G., and Wells, J. T.: <i>Surg., Gynec. & Obst.</i> 64 : 239, 1937.....	3,526	8.2
Sprague, E. W., and others: <i>Surg., Gynec. & Obst.</i> 66 : 166, 1938.....	1,436	2.7
Ray, B. S.: <i>New York State J. Med.</i> 38 : 412, 1938.....	886	2.14
Strauss, A., and Tomarkin, J.: <i>Surgery</i> 3 : 111, 1938.....	1,325	4.3
Morse, L. J., and Rader, M. J.: <i>Ann. Surg.</i> 111 : 213, 1940.....	8,727	2.15
Nassau, C. F.; Lorry, R. W., and Pulaski, E. J.: <i>Arch. Surg.</i> 42 : 296 (Feb.) 1941.....	4,650	3.2
Jennings, Burger and Jacobi: Present report, 1942.....	1,680	1.9

These patients were handled, as far as could be determined, in a manner identical with those on whom operation was performed by day and by the same surgeons and nurses, working with better less crowded operating room facilities than by day. It is further of interest that in each case in which death occurred, the operating surgeon was one of the more active men on service. There was no essential difference in

13. In our experience no patient died in the operating room or as a direct result of operation.

the severity of the disease noted in these patients or in the duration of symptoms as compared with the patients operated on by day. It seems to us that the factor of fatigue on the part of the surgeon and his staff, including nurses, may have some bearing on the fatal outcome of such cases.¹⁴ The further factor of fatigue on the part of the patient operated on during these hours, as well as postcibal activity of the digestive tract, may be of additional importance in this connection. In any event, these figures suggest that it may be advisable, in the absence of signs suggesting spreading peritonitis, to postpone operative intervention until morning and to attempt to provide rest and supportive treatment for the patient and rest to the surgical team until then.

TREATMENT

Of our 1,680 patients with acute appendicitis, all but 8 were operated on as soon as hospitalized. The latter 8 patients were treated conservatively because of the long clinical history and the clinical evidences of fulminating spreading peritonitis. Of these patients, 1 died. Of the 7 patients who recovered, the stay in the hospital after operation averaged twenty-four days.

The anesthesia used for all patients in this series was of the spinal type except for children under 12 years of age and patients with cardiac or other specific contraindications. In the latter group, numbering 321, cyclopropane or open ether was used. There were no direct anesthetic complications in any case in this series, except possibly in 2 cases of aseptic meningitis, in both of which the patients recovered without residua.

It is our opinion that one of the important factors in the low morbidity, and perhaps in the low mortality, rate in our series was the operative procedure employed. In 1,567 cases, the approach was by the McBurney incision, the length of the incision never exceeding 4 inches (10.2 cm.). The root of the appendix was easily located by palpation of the cecum, and in most cases the appendix was easily mobilized and delivered. The mesoappendix was ligated with no. 2 chromic catgut suture and cut without clamping. The base of the appendix was then rapidly crushed with a clamp and tied, and generally a purse string suture was placed in the serosa of the immediately adjacent cecum. (No cecal abscesses resulted.) The appendix was then removed with a phenolized scalpel after thoroughly protecting the skin edges and structures adjacent to the appendix with gauze, the stump was inverted into the cecum, and the purse string suture tied. No other peritonealizing procedure was employed. No wipes or packs were ever introduced into the peritoneal

14. Dr. David Kershner, attending surgeon on the staff of Beth-El Hospital, called our attention to this factor.

cavity; fluid was drained, when necessary, by suction. Drainage was resorted to only when turbid foul-smelling peritoneal fluid or localized abscess was found; when the latter was observed, the appendix was removed only if it presented itself on opening the abdomen; no attempt to find it was made. In doubtful instances, drains were not used. In all, there were 124 cases in this series in which drainage was done. The drains were not disturbed until they had been loosened by the discharge itself, usually from four to seven days after operation. Thereafter, they were elevated on loosening and removed, as a rule on the following day. The drains used were of the cigaret type. Dextrose and physiologic solution of sodium chloride were used freely, by the subcutaneous or the intravenous route or both, in generous amounts on the suspicion that fluids and electrolytes needed replacement. We did not wait for frank clinical evidences of dehydration. Morphine, to the point of narcotism, was used routinely during the first twenty-four hours after operation and in sedative doses for several days thereafter. We do not believe that this drug was in any way responsible for the intestinal obstruction encountered in a few cases of this series, and we are firmly of the opinion that the total somatic, intestinal and psychic rest so obtained was of considerable importance in obtaining our results. Patients were usually allowed to sit up on the eighth day, to be out of bed on the ninth and were discharged on the tenth day.

We feel that considerable emphasis should be laid on the McBurney approach since the right pararectus approach is still generally utilized to a greater extent than the McBurney except in cases in which the diagnosis of acute appendicitis is so positive before operation that the possibility of error is excluded. We have felt that since the appendix accounts for the preponderance of acute abdominal episodes requiring operation, and since the symptom pattern in the abdomen due to acute appendicitis is fairly distinct, that the McBurney route, allowing for rapid local exploration with the minimum of intraperitoneal disturbance, is both ideal and most practical, and this our surgical staff has routinely employed on suspicion, rather than certainty, that acute appendicitis was present. In those instances in which, on opening the abdomen along the McBurney route, the appendix was thought not to be involved, it was found easy and a matter of but a few moments to close the incision and thereafter through a new paramedian incision, so placed as not to approach intimately the McBurney incision, to explore the abdomen. In rare instances, the new incision was revised from the McBurney incision. In all, there were but 28 patients in this series requiring such treatment. In none of these cases, apparently, was the morbidity affected by the double procedure, and none of the patients died. We prefer this method of approach to that of revising the McBurney incision in cases in which an incorrect diagnosis has been made, since the lower part of

the abdomen, usually uninvolved in such cases, is kept separate from the seat of the disease, and any peritonitic process can more easily be kept local. In 36 cases in this series, in which the diagnosis was not suspected before operation, a pararectus incision was used. In such cases, however, though included in this series on the basis of the disease found, the operation was really considered as an exploratory laparotomy.

With the McBurney approach, the average time of operation in cases not complicated by abscess was twenty minutes from beginning to and including closure of the peritoneum. (The latter was closed separately from the muscles and the skin.) With a little practice it was found possible satisfactorily by palpation to explore the pelvic organs and the lower part of the abdomen through this incision in cases in which an error of diagnosis had been made before closing the incision preparatory to reentering the abdomen for further exploration as described.

We believe, further, that the McBurney approach used so regularly by our surgeons accounts for the low incidence of local wound infections (12 cases), evisceration (3 cases), abdominal cellulitis (1 case), subcutaneous hematoma (1 case) and postoperative fistula (3 cases) as complications in this series (table 4). Parenthetically, it may be noted that, except in the case of the 1 patient with postoperative evisceration (through a pararectus incision), who died (table 4), all complications were completely healed before the patient left the hospital. We have not seen any postoperative hernia in this series in cases followed for two to seven years after operation.

SUMMARY

A clinicopathologic study of 1,680 consecutive cases of acute appendicitis is presented.

It is pointed out: (1) that in cases in which mural lymphangitis and arteriophlebitis are present as complications the morbidity and mortality rates are lower than in cases in which these complications are absent (these complications are viewed as localizing defense reactions); (2) that the morbidity and mortality rates rise with the increase in the time interval between onset of symptoms and operation; (3) that catharsis is apparently a prominent factor in cases in which death occurs; (4) that preoperative chills are not of serious prognostic import.

It is suggested that the factor of fatigue on the part of the operating room team and the surgeon and on the part of the patient may be important in bringing about the death of the patient. It is suggested that after hospitalization and diagnosis, night operations be avoided in the absence of signs of spreading peritonitis in order to overcome these factors and to adjust the frequently disturbed fluid-electrolyte balance of the patient.

Particular emphasis is laid on the recommendation of the wider use of the McBurney incision, even in cases in which acute appendicitis is not rigidly diagnosed but only suspected. The advantages of such an approach with a secondary incision on recognition of the error in cases in which an erroneous diagnosis has been made are pointed out.

The symptoms, the signs, the laboratory data, the complications and the causes of death in these cases are recorded and analyzed.

The mortality rate in this series, 1.9 per cent, is compared with those of other recorded large series.

The question of causation is briefly discussed.

The rigid criteria for the diagnosis of acute catarrhal appendicitis are given, and it is stressed that these should be followed in evaluating any statistical studies relative to mortality rate of appendicitis.

It is pointed out that fluids and electrolytes should be given freely without waiting for clinical evidences of disturbed balance.

Some of the cases used in this study are included with the permission of members of the surgical staff of Beth-El Hospital. Mr. Morrell Goldberg, record librarian and assistant superintendent, assisted in compiling the data.

POLYPOSIS OF THE VERMIFORM APPENDIX

REPORT OF A CASE

S. SANES, M.D.

AND

DANIEL F. PATCHIN, M.D.

BUFFALO

No other intra-abdominal organ receives such routine surgico-pathologic examination as the vermiform appendix. One might wonder, then, whether there could exist any appendical lesions the discovery of which would elicit surprise. Yet, polyposis of the vermiform appendix is so rare that observation of a single example of this condition is taken as justification for the following report.

REPORT OF CASE

H. P., a 20 year old white handy man, was admitted to the Niagara Falls Memorial Hospital to the service of Dr. Norman J. Eick on Jan. 26, 1940, with the complaints of vomiting and abdominal pain. He was discharged February 17.

The patient had been in good health until 1936. At that time he began to have attacks of vomiting. These occurred once or twice a week. Emesis usually followed half an hour after a meal. Along with vomiting, the patient suffered pain on the left side of the abdomen. At times there was pain in the right lower quadrant.

Before the patient's entry to the hospital, emesis increased in frequency, and abdominal pain became worse.

A detailed familial history contained no relevant data.

Examination.—The abdomen was distended. A freely movable tender lemon-sized mass was palpated to the left of the umbilicus. On different occasions the mass shifted in position; it was found on the right side of the abdomen and in the suprapubic region.

Röntgen Examination.—The duodenal cap was large and had a defect in the upper border. Just beyond the cap, the duodenum was not well visualized. In six hours the head of the meal reached the hepatic flexure. A little of the meal was still in the stomach and the duodenum. The terminal part of the ileum and the appendix were not visualized. There was pain with tenderness in the ceco-appendical area, which was referred upward. The colon was moderately spastic.

Laparotomy (February 5).—Through an upper right rectus incision, adhesions between the duodenum and the transverse part of the colon were released. The first portion of the jejunum was dilated; the wall was thickened. The distal part of the jejunum was collapsed. Located between the dilated and collapsed portions of the jejunum was a freely movable mass which on incision of the bowel

From the Niagara Falls Memorial Hospital.

proved to be a pedunculated polyp. After ligation of the pedicle, the polyp was excised. The appendix was removed because it was enlarged and injected.

Pathologic Description.—*Macroscopic:* The appendix measured 8 cm. in length. The average circumference was 1.1 cm. The serosa was distinctly injected. The wall, 0.15 cm. thick, was opaque. The lumen contained bloody fluid; there was no fecal matter. Originating 0.8 cm. from the proximal end of the appendix was a polyp 3.7 cm. in length and 0.5 cm. in diameter. Its surface was markedly hyperemic and hemorrhagic. Its base obstructed the proximal end of the appendix. The polyp projected toward the distal tip of the organ. Another polyp, which originated 4.1 cm. distal to the point of attachment of the first tumor, measured 1.7 cm. in length and 0.3 cm. in diameter. Its surface also was hemorrhagic. The second polyp pointed toward the proximal end of the appendix. Its base,

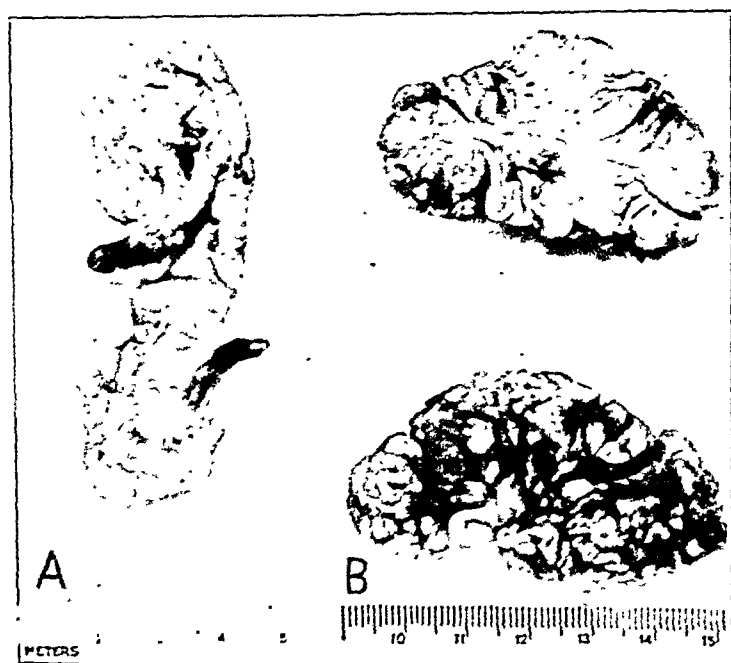


Fig. 1.—Photographs showing gross appearance (A) of the appendix with polyps and (B) of jejunal papilloma.

0.6 cm. in diameter, appeared sessile and had edges which were firm, immobile and elevated 0.75 cm. above the mucosa. The two polyps overlapped for a distance of 0.4 cm. In their combined length they filled the lumen of the appendix like a cast. Scattered on the appendical mucosa were pinhead-sized opaque elevations (fig. 1).

The specimen from the jejunum was a papillomatous polyp, 7 by 4.5 by 3 cm., attached to a portion of mucosa, 3.2 by 1.3 cm.

Microscopic: In the appendix the largest polyp represented adenoma. It was fairly rich in glands of varying sizes. Some were cystic and dilated; these compressed the adjacent glands and stroma. The lumens of the dilated glands contained fecal material, often in the form of a fecalith. Entrance of feces could be traced to openings in the surface. In some lumens there were red blood cells, neutrophils, eosinophils and mononuclear cells. In most lumens of moderate size, mucus was present. The lining of small and moderate-sized glands consisted

chiefly of a single layer of columnar cells with nearly basal oval vesicular nuclei and with tall mucous borders. Goblet cells were seen. In dilated glands which contained fecaliths, the lining was flattened in places, with hyperchromatic nuclei here and there. In the polyp, as a whole, mitotic figures were rare.

The stroma was slight. It showed edema, infiltration of plasma cells, eosinophils and neutrophils, focal collections of lymphocytes, sometimes as lymph follicles with reactive centers, and swelling of stroma cells. There were extensive recent hemorrhages.

The second polyp also was adenoma. It differed in certain respects from the largest polyp. The glands revealed more marked secretion of mucus, with dilatation of lumen and mucoid degeneration of epithelial cells. The epithelium was inflamed. Interstitial hemorrhage was greater in amount. One vein revealed parietal thrombosis. In a few glands the histologic picture was no longer altogether typical. There was epithelial proliferation within the glands. The nuclei were hyperchromatic. Mitotic figures were relatively numerous. No invasion at the bases of the polyps was seen.

Sections taken from the appendix at various levels disclosed glandular hyperplasia with dilated glands, which contained increased mucus, desquamated cells and neutrophils, in the mucosa. In some places small adenomatous elevations were noted which structurally were similar to the large polyps. The lymphatic tissue varied in amount. The outer layers of the appendix showed no inflammatory infiltration.

Jejunum: The tumor was papillomatous adenoma.

Postoperative Course.—The patient developed incisional hernia. He gave a history of the presence of red blood in the stools but refused sigmoidoscopic examination.

COMMENT

An idea of the rarity of polyposis of the vermiform appendix can be had from the fact that in 1932 Collins¹ compiled only 17 cases from the literature. To these he added what constituted the single instance (an incidental observation at autopsy) encountered in all the appendices which had been examined up to that time at the Mayo Clinic. In the past nine years, the *Quarterly Cumulative Index Medicus* has listed but 1 report of adenomatous polyp,² giving it under the heading of tumor of the appendix. (Cases of adenoma reported by Novis³ and Satanowsky⁴ are excluded because the lesions were not strictly polypous.) Perhaps polyps of the appendix might be discovered more frequently if, when examined, the surgical or autopsy specimen were cut along its entire length.

According to the information tabulated by Collins¹ from the old literature and according to the recent descriptions of Collins¹ and

1. Collins, D. C.: Adenomatous Polyps of the Vermiform Appendix, *S. Clin. North America* **12**:1063-1067 (Aug.) 1932.

2. Lastra, J.: Pólipo de apendice vermiforme, *Arch. de med. inf.* **5**:35-39 (Jan.-March) 1936.

3. Novis, A. A.: Tumor apendicular, *Bahia méd.* **4**:116-118 (June) 1933.

4. Satanowsky, S.: Invaginación crónica del apéndice por adenoma e invaginación recidivante ceco-cólica, *Rev. Asoc. méd. argent.* **54**:724-727 (April 20) 1940.

Lastra,² the available knowledge of polyposis of the vermiform appendix can be briefly summarized. Among the recorded cases, the sex incidence was given as 9 in male patients and 10 in female. In 14 patients, the ages ranged from 6 to 40 years; in 4, from 60 to 80 years. The polypous lesion was situated in the proximal third of 14 appendixes. Three specimens showed involvement of the middle third; 2, of the distal third. The majority of the polyps were small. Measurements ranged from 0.5 to 3 cm. long. Authors attributed symptoms, which varied from six weeks to over a year in duration, to the appendix in 13 cases. Four patients had no symptoms referable to the appendix. Pathologically,



Fig. 2.—Photomicrographs (A) of adenomatous hyperplasia of appendiceal mucosa ($\times 5\frac{1}{2}$) and (B) of the largest appendiceal polyp ($\times 5\frac{1}{2}$).

polyposis was associated with acute, subacute or chronic recurring appendicitis in 10 instances. In 4 cases, intussusception of the appendix and the ileocecal region had occurred. Lastra found oxyuriasis in his specimen.

On the basis of the foregoing summary of the literature, our case bears significance because of certain pathologic characteristics of its own and because of various features of polyposis of the vermiform appendix which it illustrates in general. Ordinarily a single rather small tumor has been described. Of special interest, then, is the gross presence of multiple polyps and adenomas in the appendix which we examined. The largest polyp in our specimen surpasses the maximal measurement

derived from the literature by Collins. Histologically, the findings in our polyps of fecal concretions within glands, venous thrombosis and slight atypical epithelial proliferation are noteworthy.

To the question of the genesis of polyposis of the vermiform appendix, on which there has been speculation in the literature, our case brings two concrete answers. First, development of the large polyps in our specimen can be traced to glandular hyperplasia and adenomatosis of the mucosa. The large polyps are therefore true adenomas. We can exclude their origin on the grounds of inflammation. Whether inspissated feces in glands may act as an irritative factor in mucosa with congenital disposition for adenomatosis is difficult to say.

Of further pathogenic import stands the occurrence of polyposis of the appendix in our patient with polyposis in other segments of the intestine. A large papillomatous adenoma of the jejunum produced obstructive symptoms so that operation was necessary for relief. With the history of melena, polyps were suspected in the rectum and the colon. Pathogenetically, the existence of appendical polyps as part of polyposis of the gastrointestinal tract in the absence of chronic ulcerative enterocolitis supports the neoplastic theory of origin on the basis of congenital disposition of the mucosa. Curiously enough, systematic investigations of the not uncommon condition of polyposis of the colon fail to mention the incidence of involvement of the appendix. In Collins' case there were multiple polyps of the colon with carcinoma of the sigmoid flexure. Recently, Olson⁵ demonstrated small adenomatous polyps in the appendix of a 24 year old man who suffered with hereditary familial polyposis of the colon and who died from malignant change in one polyp with metastases. In our case, no hereditary history was established through questioning the patient.

Clinically, the implications of the involvement of the appendix in polyposis of the gastrointestinal tract carry practical responsibilities. Before symptoms are completely explained on the basis of polyposis of the appendix, removed through a McBurney incision and, what is more important, before prognosis is made on the sole basis of the appendical lesion (even if the polyps are discovered merely by accident), polyposis of the stomach, the small intestine and the large bowel should be searched for. Witness our case in which polyps were demonstrated in the small intestine and were suspected from the history in the large bowel. Isolated polyposis of the appendix forms the contrasting type.

Preoperative diagnosis of polyposis of the appendix seems impossible. Discovery of this lesion is a laboratory incident. From a speculative standpoint, however, polyps of the appendix might con-

5. Olson, K.: Personal communication to the authors.

ceivably produce pathologic complications and through these, possibly, clinical symptoms. In our case the largest polyp obstructed the proximal portion of the appendix: both polyps filled the appendical lumen, except for its distal part, in castlike manner. In the roentgenograms, the appendix did not fill with barium sulfate. At times our patient complained of pain in the right lower quadrant. The question arises whether polyps of the appendix may cause obstructive symptoms by their size and position. Further, may the obstruction brought about by a polyp act as a determining factor in the genesis of appendicitis? We have already referred to actual cases of intussusception of the appendix and the ileocecal region in which the process was apparently dependent on the peristaltic attempt of the appendix to extrude from its lumen a polyp which represented an obstructing foreign body.

The pathologic specimen in our case suggested how polyposis of the appendix, when it is an isolated lesion and when it does not prevent emptying of the appendical content, may reasonably serve as a rare obscure source of blood in the stool. The content in our appendix consisted of fluid blood. Of course, surgical manipulation brings about hemorrhage into the mucosa and the lumen of the appendix. But appendical polyps themselves, just as polyps of the colon, possess the potentialities for bleeding in erosions of the surface, interstitial hemorrhages, strangulation of pedicle and vascular thrombosis.

Adenomatous polyps of the stomach and colon are notorious for their tendency to become malignant. While carcinoma has not been reported in polyposis of the appendix, it has been assumed that appendical polyps may also undergo malignant change. In one of the polyps in our specimen, glands showed slight signs of atypical epithelial proliferation but no infiltration. On the basis of the possibility of malignant transformation, Collins justified removal of an appendix with polyposis.

76 Butler Avenue.

NEW DIAGNOSTIC POINTS IN APPENDICITIS

A CLINICOANATOMIC CONSIDERATION OF BILATERAL HYPERALGESIA

MATTHEW S. LEVITAS, M.D.

BROOKLYN

Evidence of appendicitis has been discovered in mummies of ancient Egypt.¹ The earliest description of the anatomy of the appendix was recorded in 1524 by Jacopo Berengario da Carpi.² Vesalius in 1543 termed it the cecum or blind sac. Ambroïse Paré in 1582 stated that the intestine has a long and narrow apophysis, but it is believed that Fallopius in 1561 was the first to compare the appendix to a worm.³ In the nineteenth century renewed interest aroused by the description of Gerlach's valve (1847), Treitz's pericecal fossa (1857) and Clado's ligament (1892) was followed by an active era of clinical, therapeutic and operative progress which is associated with many noted clinicians.

Somatic nerve distribution received early physiologic consideration by Gaskell.⁴ He described the origin of the nerves in the spinal segments of animals as having somatic and splanchnic roots. On the basis of clinical observations of various diseases in man, Ross⁵ described the regional distribution of somatic and splanchnic pain. Head's⁶ classification of various diseases in man on a segmental basis has since received general acceptance. The conception of an overlapping of spinal segments was advanced by Sherrington,⁷ Mackenzie⁸ and Langley.⁹ Mackenzie^{8a}

From the Department of Surgery, Israel-Zion Hospital.

1. Bett, W. R.: *A Short History of Some Common Diseases by Divers Authors*, London, Oxford University Press, 1934, pp. 162-171.

2. Deaver, J. B.: *Appendicitis: Its Diagnosis and Treatment*, ed. 3, Philadelphia, P. Blakiston's Son & Co., 1905.

3. Royster, H. A.: *Appendicitis*, New York, D. Appleton and Company, 1927.

4. Gaskell, W. H.: *On the Structure, Distribution and Function of the Nerves Which Innervate the Visceral and Vascular Systems*, *J. Physiol.* **7**:1, 1886.

5. Ross, J.: *On the Segmental Distribution of Sensory Disorders*, *Brain* **10**: 333, 1888.

6. Head, H.: *A Disturbance of Sensation with Especial Reference to the Pain of Visceral Disease*, *Brain* **16**:1, 1893.

7. Sherrington, C. S.: (a) *Experiments in the Examination of the Peripheral Distribution of the Fibers of the Posterior Roots of Some Spinal Nerves*, *Proc. Roy. Soc., London* **52**:333, 1892-1893; (b) *The Integrative Action of the Nervous System*, New Haven, Conn., Yale University Press, 1923, p. 254.

8. Mackenzie, J.: (a) *Associated Pain of Visceral Disease*, *M. Chron.* **16**: 295, 1892; (b) *The Nature of the Symptoms in Appendicitis*, *Brit. M. J.* **2**:66

(Footnotes continued on next page)

proposed the theory that the spinal reflex consists of a visceromotor and a viscerosensory component.

Sensory involvement in appendicitis has been found to extend above and below the level of the distribution of the dorsal eleventh spinal nerve.⁸ In July 1903, Mackenzie⁹ stated that the nerve involvement in appendicitis can be grouped within the field supplied by the eleventh and twelfth dorsal and the first and second lumbar nerves. In September 1903, Sherren¹⁰ found a somatic band corresponding to the dorsal eleventh nerve, tenderness often extending to the dorsal tenth and occasionally the dorsal twelfth nerve. He also described a triangular area of sensitiveness in the right lower quadrant of the abdomen. Robinson¹¹ in 1908 observed cutaneous tenderness of the dorsal eleventh nerve in appendicitis but sometimes of the ninth, tenth and twelfth dorsal and possibly of the dorsal eighth and lumbar first segments. Livingston¹² in 1923 described an appendicular triangle of tenderness extending to the umbilicus.

TABLE 1.—*Maximum Hyperalgesia of Spinal Nerves in Cases of Appendicitis*

Spinal Nerve	Right Side	Left Side
Dorsal 11.....	55	53
Dorsal 5.....	1	1
Lumbar 1.....	1	1
Negative.....	2	4

It may be stated that in my experience the dorsal eleventh nerve is mainly concerned in the somatic distribution of hyperalgesia in appendicitis (table 1). This is in accord with the opinion of other observers also.¹³ McBurney's point¹⁴ and his description of appendicitis as a

(July 11) 1903; (c) Some Points Bearing on the Association of Sensory Disorders and Visceral Disease, *Brain* **16**:321, 1893; (d) Symptoms and Their Interpretation, London, Shaw & Sons, 1909; (e) Herpes Zoster and the Limb Plexuses of Nerves, *J. Path. & Bact.* **1**:332, 1893.

9. Langley, J. N.: Preliminary Account of the Arrangement of the Sympathetic Nervous System, Based Chiefly on Observations upon Pilo-Motor Nerves, *Proc. Roy. Soc., London* **52**:547, 1892-1893.

10. Sherren, J.: On the Occurrence and Significance of Cutaneous Hyperalgesia in Appendicitis, *Lancet* **2**:816, 1903.

11. Robinson, H.: The Clinical Bearing of Cutaneous Tenderness on Various Acute Abdominal Disorders, Especially Appendicitis, *Quart. J. Med.* **1**:387, 1908.

12. Livingston, E. M.: The Skin Signs or Viscerosensory Phenomena in Acute Appendicitis, *Arch. Surg.* **7**:83 (July) 1923.

13. Head.⁶ Mackenzie.⁸ Sherren.¹⁰ Robinson.¹¹

14. McBurney, C.: Experience with Early Operative Interference in Cases of Disease of the Vermiform Appendix, *New York M. J.* **50**:678, 1889.

clinical entity have long received the widest clinical acceptance. There are other points of tenderness which lie within close range of the dorsal eleventh spinal nerve, in or near the rectus muscle. Other observers subsequently described such points of tenderness in appendicitis, viz., Lotheissen,¹⁵ Lanz¹⁶ and Clado.¹⁷ Clado's point is located at the intersection of both anterior superior spinous processes and the lateral border of the right rectus muscle. Lanz's point is similar to this except that it is located where the right and middle thirds of the interspinous line join. Morris' point¹⁸ is somewhat higher up. Gray¹⁹ mentioned a left-sided point which is about 1½ inches (3.75 cm.) below and to the left of the umbilicus and which he stated corresponds to the emergence of the terminal branches of the dorsal eleventh nerve. Deaver² stressed the importance of Clado's point on the basis of personal observations.

Mertens²⁰ compared McBurney's and Lanz's point in 309 patients with the following results: 27 were tender at McBurney's point only; 88, at both, and 194, at the Lanz point only.

Deep hyperalgesia has been recognized as a clinical sign. The causal relation has been regarded as a pressure on nerve twigs. Small branches of the eleventh and twelfth nerves pierce the rectus muscle, and tenderness is elicited by pressure on these nerve twigs.⁸

Bilaterality of hyperalgesia has been mentioned by various observers, viz., Head, Mackenzie, Sherren and Gray.¹⁹ They stated that a reflex on the contralateral side may be present in appendicitis. Mackenzie found it difficult to conceive of the appendicular reflex as being unilateral.

Paravertebral block for diagnostic purposes has been used by other observers and myself. They are mentioned by Hewer.²¹ Nerve block has abolished pain in gallbladder disease without any effect on pain from adjacent viscera (Rosenthal). It has also been used for acute pancreatitis (Popper) and for angina pectoris (Mandl).

The present study is based on the observation of tender points in appendicitis and the distribution of hyperalgesia above and below the

15. Lotheissen, cited by Whipple, A. O., in *Nelson Loose-Leaf Living Surgery*, New York, Thomas Nelson & Sons, 1928, vol. 5, p. 315.

16. Lanz: *Der McBurney'sche Punkt*, *Zentralbl. f. Chir.* **1**:185, 1908.

17. Clado: *Appendice caecal*, *Compt. rend. Soc. de biol.* **44**:133, 1892.

18. Morris, R. T.: *Metaplasia of the Appendix Vermiformis and a New Diagnostic Point*, *New York M. J.* **87**:1060, 1908.

19. Gray, H.: *Physical Factors in the Production of Appendicitis. Points in Diagnosis: Their Influence on Surgical Treatment*, *Illinois M. J.* **48**:36, 1925.

20. Mertens, V. E.: *Der Lanzasche Punkt und seine Bedeutung für die Erkennung des Wurmfortsatzes als Gesundheitsstöres*, *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* **33**:557, 1921; cited by Royster.³

21. Hewer, C. L.: *Recent Advances in Anaesthesia and Analgesia*, ed. 3, Philadelphia, The Blakiston Company, 1939, p. 165.

dorsal eleventh nerve. In addition, a detailed study has been made of bilateral tender areas. Paravertebral injection as a diagnostic aid has been utilized in blocking out the several symptoms and signs in appendicitis. This work is a continuation of a previous study dealing with the clinicoanatomic findings in diseases of the urogenital tract.

The clinical study consisted of 60 consecutive cases of appendicitis from the surgical service of the Israel-Zion Hospital and also my private cases and those of my associates. Many additional cases subsequently examined are not included in this series, although they are confirmatory of the results, hereinafter to be recorded. Acute appendicitis with a tense or rigid abdomen has been obviously omitted. These cases are classified as follows: 37 cases of chronic appendicitis, 14 of acute, 4 of subacute, 3 of appendicular abscess and 2 of subsiding appendicitis. There were 38 female and 22 male patients. In 49 cases, the age incidence was from 10 to 30 years. Appendectomy was performed in 55 cases and incision and drainage in 3 cases.

Six of the patients had gangrenous appendicitis: 2 out of 5 patients with retrocecal appendicitis complained of urinary symptoms, and 4 patients had associated ovarian disease—either one condition or the other being primary. The diagnosis of appendicitis was based on the operative findings as recorded by the surgeon. The gross and microscopic pathologic reports (made by Dr. J. M. Ravid, the pathologist of the Israel-Zion Hospital) were used for confirmation of diagnosis.

ANATOMY OF THE ABDOMINAL WALL

The fleshy part of the external oblique muscle can usually be felt in the lateral abdominal wall as a rounded edge by rolling it under the examining fingers. The interval between the fleshy edge and the lateral border of the rectus abdominis muscle, for convenience, has been termed the fascial space. It is the aponeurosis of the external oblique muscle.

On leaving the thorax between the eleventh and twelfth ribs, the dorsal eleventh nerve lies between the transversus and obliquus internus muscles. At this point in the lateral abdominal wall, the termination of the twelfth or floating rib exposes the dorsal eleventh nerve, making it more accessible to the pressure of the examining fingers. It crosses under the fleshy margin of the external oblique muscle about on a level with the umbilicus. Then it courses obliquely downward to pierce the rectus abdominis muscle at the edge or slightly mesial to its lateral border and on its deeper aspect, about on a line with the anterior superior spine of the ilium. The dorsal eleventh nerve eventually reaches the anterior abdominal wall and becomes cutaneous by piercing the rectus muscle.²²

22. Cunningham, D. J.: *Text-Book of Anatomy*, edited by A. Robinson, ed. 5, New York, William Wood & Company, 1928, p. 746.

RELATION OF TENDER POINTS TO NERVE DISTRIBUTION

In palpation of the tender points observed in appendicitis, I elicited deep hyperalgesia instead of the lighter tactile method used by Head, Mackenzie and Sherren or the vigorous twisting pinch of Livingston.

Pressure pain is a form of deep sensibility. It can be elicited normally by applying pressure over nerve trunks.²³ The various spots palpated bilaterally were: first, at the tip of the twelfth rib; second, at the mesial edge of the fleshy part of the external oblique muscle about on a level with the umbilicus, and, third, somewhat mesial to the lateral margin of the rectus muscle on a level with the anterior superior spine of the ilium (illustration). These spots were tender to palpation and were found to correspond to the underlying dorsal eleventh spinal nerves.

FINDINGS

Tender Points.—The six points of bilateral tenderness just enumerated may be further described as follows (illustration):

Right Side: 1. The first point is in the eleventh intercostal space and is elicited by pressure of the examining fingers at the tip of the twelfth rib.

2. The second point is slightly mesial to the lateral margin of the rectus abdominis muscle about on a level with the anterior superior spine of the ilium.

3. If a line is drawn between the first and second points, the intersection of this line by the mesial margin of the fleshy part of the external oblique muscle represents the third point. This is frequently located on a level with the umbilicus.

Left Side: There are three analogous points on the left side, making a total of six.

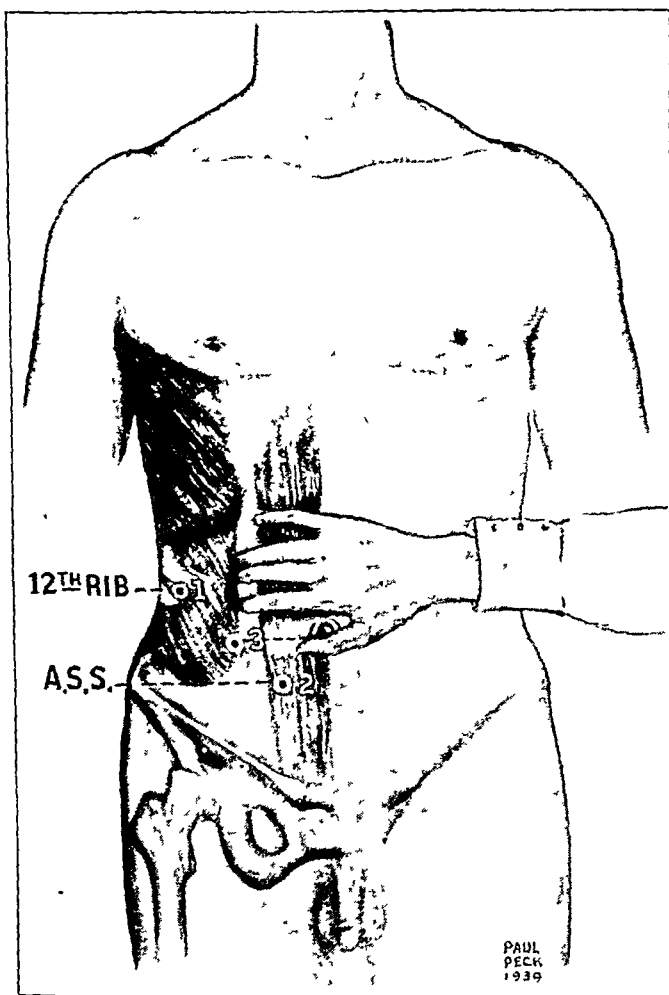
These six points vary also in the comparative degree of individual sensitivity in a given case. The second point, or the one in the body of the rectus muscle, usually evidenced the maximum degree of hyperalgesia. The fascial space was least tender.

Bilaterality.—The contralateral reflex was observed in 95 per cent of the cases proved to be cases of appendicitis. This percentage may appear high. Yet, it was obvious that three different points of tenderness were present on the left side. In all instances of bilaterality in this series, contralateral tenderness of the three points was noted in the majority of cases, less frequently two points and but rarely one point.

It may be generally stated that on the contralateral side a lesser number of nerves was involved and that the reaction was less intense

23. Bing, R.: *Compendium of Regional Diagnosis in Lesions of the Brain and Spinal Cord*, translated and edited by W. Haymaker, ed. 11, St. Louis, C. V. Mosby Company, 1940, p. 30.

than on the homolateral side. In case 33 (table 4), on the right side the involvement extended from the dorsal fifth to the lumbar second nerve, while on the left side it extended from the dorsal tenth to the lumbar second nerve, ten nerves being affected on the right side and six on the left. The comparative reaction of the dorsal eleventh nerve was 2 plus²⁴ on the right side and 1 plus on the left. The maximum



Points of tenderness (1, 2 and 3) in appendicitis. A. S. S., anterior superior spine of the ilium.

reaction, bilaterally, was noted in the dorsal eleventh nerve as compared with all other spinal nerves involved.

Paravertebral Injection (table 2).—The blocking in the region of the right dorsal eleventh nerve afforded an opportunity for studying its

²⁴. One plus indicates slight hyperalgesia; 2 plus, moderate, and 3 plus, maximum.

effect on the various tender spots, hereinafter recorded, in a recognized case of appendicitis. The additional subsidence or disappearance of associated symptoms also was noted.

REPORT OF A CASE

H. T., a young man 18 years of age, was admitted to the Israel-Zion Hospital on July 22, 1937. Two days before admission, the patient experienced intense pain in the right upper part of the abdomen which gradually localized in the right lower part. He was free from pain for a period of several hours, when another

TABLE 2.—*Somatic Hyperalgesia * Before and After Paravertebral Injection of 5 cc. of a 2 per Cent Solution of Procaine Hydrochloride into the Right Dorsal Eleventh Nerve*

Location	Right Side				Left Side			
	Before Para-vertebral Injection	After Para-vertebral Injection (25 Min.)	Before Operation	After Operation (11 Days)	Before Para-vertebral Injection	After Para-vertebral Injection (25 Min.)	Before Operation	After Operation (11 Days)
Dorsal 1 to 6 ..	0	0	0	0	0	0	0	0
Dorsal 7. ..	+ -	0	0	0	0	0	0	0
Dorsal 8 ..	+ -	- +	+ -	0	+ -	0	0	0
Dorsal 9	+ -	- +	+ -	0	+ -	0	0	0
Dorsal 10	+ -	0	0	0	+ -	0	0	0
Dorsal 11 .	1+	0	0	0	+ -	0	0	0
Dorsal 12	+ -	0	0	0	0	0	0	0
Lumbar 1 . . .	+ -	0	0	0	0	0	0	0
Lumbar 2.	+ -	0	0	0	0	0	0	0
First point: Eleventh intercostal space at tip of the twelfth rib..	1+	0	0	0	0	0	0	0
Second point: Rectus abdominis muscle slightly mesial to the lateral margin and about on a level with the anterior superior spine of the ilium..	1+	0	+ -	- +	+ -	0	+ -	- +
Third point: Edge of the external oblique muscle. . .	1+	0	+ -	- +	+ -	0	+ -	- +

* + - signifies very mild hyperalgesia; - +, doubtful or inconstant.

attack was precipitated after playing a game of handball while at work. During his subsequent twenty-four hour stay in the hospital, the pain recurred, starting in the right lower part of the abdomen and radiating to the upper part of the abdomen. He also felt a soreness in the lower right part of the chest posteriorly. Nausea but no vomiting was present. On examination there was more marked spasm of the rectus muscle and tenderness in the right lower part of the abdomen than in the upper. Tenderness of the dorsal seventh to the lumbar second spinal nerves on the right side and of a lesser number of nerves on the left side and of the six points previously described was observed. The maximal tenderness was noted in the dorsal eleventh nerve.

On July 23 at 11:40 a. m., the patient received a paravertebral injection of 5 cc. of 2 per cent solution of procaine hydrochloride in the region of the right dorsal eleventh spinal nerve.

At 11:45 a. m., the patient experienced no pain in the abdomen or the back and no soreness of the lower part of the chest. On deep breathing, however, he felt a slight pain in the back.

At 12 noon, pain had disappeared in all regions, including the epigastrium, the hypogastrium, the chest and the back.

At 12:05 p. m., no tenderness over the upper rectus muscle or the abdomen was elicited bilaterally. All pain had disappeared anteriorly and posteriorly.

At 12:15 p. m., no tenderness along the entire right or left rectus muscle was present. The rectus muscle was in a state of relaxation although it had been spastic before the paravertebral injection.

At 12:45 p. m., the patient felt some soreness in the right lower part of the chest and the right epigastrium but no pain in the right or the left lower part of the abdomen. There was no soreness felt posteriorly.

At 1 p. m., moderate soreness was perceived in the right upper part of the abdomen and to a lesser degree in the lower part of the abdomen. The pains in the left lower portion of the abdomen also were returning.

On July 24, prior to operation and the day subsequent to the paravertebral injection, pain in the back, the lower part of the chest and the abdomen as well as nausea was gone. There was occasional pain in the right lower part of the abdomen.

On July 24, appendectomy was performed. The appendix was 2 inches (5 cm.) long and retrocecal. The mesoappendix was short. A moderately thickened membrane covered the distal $\frac{3}{4}$ inch (1.88 cm.) of the appendix, fixing the appendix to the cecum. As a result of this constriction band, there was a pressure atrophy of the distal part of the appendix, diminishing the caliber and the lumen of the appendix. The pathologist reported that there was moderate injection of the serosal vessels, and on microscopic examination the wall was found to be atrophic and to contain dense fibrous connective tissue. The appendix contained two soft fecoliths. Pathologic diagnosis was atrophic appendicitis.

On the day following paravertebral injection and prior to operation (table 2), the patient who had received a paravertebral block presented fewer and considerably less tender nerves and also an amelioration of symptoms. Eleven days after appendectomy, all spinal nerve tenderness, bilaterally, had disappeared except the latter two of the three diagnostic points, which remained barely sensitive to pressure. It is obvious that nerve tenderness had almost completely disappeared.

ANALYSIS OF THE APPENDICULAR REFLEX

In 6 patients, or 10 per cent of the 60 cases, involvement of the dorsal eleventh nerve only, unilaterally or bilaterally, was noted. No other spinal nerve was affected. Hyperalgesia of the dorsal eleventh nerve alone may therefore be considered to represent, I believe, a pure appendicular reflex, which I have termed a minimal reflex and which may occur unilaterally or bilaterally. The reflex in the remaining 90 per cent of the cases was bilateral, involving more than one nerve and termed a maximal reflex.

The comparative degree of hyperalgesia in the spinal nerves was noted bilaterally. A maximal reaction in the eleventh dorsal nerve as

compared with the other spinal nerves occurred on the right side in 55 cases, 91.7 per cent (table 1), and on the left side in 53 cases, 88.3 per cent.

THE UPPER AND LOWER LIMITS OF HYPERALGESIA IN APPENDICITIS

A study of the upper limits of bilateral hyperalgesia has been recorded in each individual case in this series (table 3 A). In table 3 B, the lower limits are shown. Comparison of the two parts of the table reveals a more extensive distribution on the right than on the left side, above and below the dorsal eleventh nerve. In addition, on the left side the nerves were considerably less tender.

Analysis of table 3 reveals the extension of hyperalgesia to the upper dorsal segments. This would appear to be a wider diffusion than is

TABLE 3.—*Upper and Lower Limits of Hyperalgesia of Spinal Nerves Above and Below the Dorsal Eleventh Nerve*

A. Upper Limits			B. Lower Limits		
Spinal Nerve	Right side	Left Side	Spinal Nerve	Right Side	Left Side
Dorsal 3.....	1		Dorsal 11.....	22	31
Dorsal 4.....	1		Dorsal 12.....	15	11
Dorsal 5.....	6	1	Lumbar 1.....	10	5
Dorsal 6.....	3	1	Lumbar 2.....	10	7
Dorsal 7.....	1	0			
Dorsal 8.....	4	0			
Dorsal 9.....	7	6			
Dorsal 10.....	20	14			
Dorsal 11.....	15	31			
Total.....	58	53	Total.....	57	54

generally reported in cases of appendicitis. However, the clinical picture in this series of cases included the classic symptoms and signs, and the pathologic findings were corroborative. Follow-up observations were not possible in all instances. Whether coexisting conditions other than appendicitis are to be considered in the cases of extreme distribution of hyperalgesia merits further study.

These observations, aided by paravertebral block and postoperative disappearance of the previously enumerated tender spots and disseminated hyperalgesia and associated symptoms, strongly suggest the intimate relation of hyperalgesia as hereinbefore classified to appendicitis.

COMMENT

Differential Diagnosis ³.—Though reliance on these signs is valuable, it has its limitations. Recognition must be given to certain forms of radiculitis which often produce a confusing symptom complex, viz.,

radiculoganglionitis as described by Davis²⁵ in children or herpes zoster before the rash appears. Radiculitis may occur also secondary to osseous vertebral changes,²⁶ and subcostal neuritis,²⁷ secondary to pressure of the twelfth rib on the bony pelvis. Pathologic conditions in the abdominal wall also must be differentiated, e. g., rupture of the right rectus muscle²⁸ or hemorrhage into the right rectus muscle sheath.²⁹

General Observations.—Maximal hyperalgesia has been observed to become minimal or to disappear in cases of subsiding appendicitis, after appendectomy and after paravertebral injection.

In several patients with appendicitis operated on by me, the appendix was not located directly under or even in the vicinity of the maximal point of hyperalgesia in the abdominal wall. This is in accord with the opinions of Pottenger,³⁰ Sherren, Mackenzie and Burgess.³¹ The last named studied 500 cases.

In 1 of the cases of acute gangrenous appendicitis there was but slight hyperalgesia of the dorsal eleventh spinal nerve of the right side, although rebound tenderness was present. In comparison with the advanced pathologic findings, the symptoms and the abdominal signs were relatively mild—a not unusual experience in cases of acute gangrenous appendicitis.

A difficulty frequently encountered in diagnosis is the differentiation of retrocecal appendicitis from lesions of the urogenital tract. A comparison of the tender points previously described in diseases of the ureter³² with those of appendicitis was found to be of value in establishing a diagnosis. Such differential diagnosis is frequently aided by the comparative predominance of the tender points peculiar to appendicitis.

25. Davis, J. H.: Segmental Neuralgia in Childhood Simulating Visceral Disease, *J. A. M. A.* **107**:1620 (Nov. 14) 1936.

26. Campbell, W. F.: *Surgical Anatomy*, Philadelphia, W. B. Saunders Company, 1921.

27. Clinton, M.: Subcostal Neuritis as a Cause of Abdominal Pain, *J. A. M. A.* **83**:90 (July 12) 1924.

28. Wohlgemuth, K.: Ueber die subcutane Ruptur des M. rectus abdominis und der Arteria epigastrica (spontanes Bauchdeckenhämatom), *Arch. f. klin. Chir.* **122**: 649, 1922.

29. Danzis, M., and Soschin, S.: Spontaneous Hemorrhage Within Right Rectus Sheath Simulating Acute Appendicitis, *S. Clin. North America* **6**:1421, 1926.

30. Pottenger, F. M.: *Symptoms of Visceral Disease*, ed. 5, St. Louis, C. V. Mosby Company, 1938.

31. Burgess, A. H.: An Analysis of Five Hundred Consecutive Operations for Acute Appendicitis, *Brit. M. J.* **1**:415, 1912.

32. Levitas, M. S.: Tender Points in Diseases of the Renal Pelvis and of the Ureter: Peripheral Distribution of Unilateral and Bilateral Hyperalgesia and Anatomic Relations of the Spinal Nerves and Muscles Involved, *Arch. Surg.* **39**:457 (Sept.) 1939.

Since the present study is preliminary, further work will be required with a larger series of cases of retrocecal appendicitis before a final opinion can be given.

Somatic Distribution of the Appendicular Reflex.—The somatic distribution of the appendicular reflex may be transmitted by way of longitudinal and/or transverse muscle segments in which intersegmental anastomosis of the peripheral nerves may take place. In the thorax there is anastomosis of the intercostal nerves.³³ In the lateral abdominal wall between the transversus and obliquus internus abdominis muscles, anastomosis may take place by way of the lower four dorsal nerves (Hovelacque). I have described likewise such an intersegmental anastomosis of the lower four intercostal and first lumbar nerves, some of which I have found in addition to be intimately connected by way of a plexus formation, looping and nerve termination around the deep circumflex iliac artery.³² Fusion of the segmental myotomes in the longitudinal posterior muscles, which are supplied by a series of muscular branches derived from the posterior rami of contiguous nerves, has been described.²² That a similar anastomosis may take place in the posterior muscles of the abdominal wall, viz., the psoas and the iliacus muscle groups, merits study. Davies and associates³⁴ pointed out that any nerve in the region of the rectus abdominis muscle contains fibers from at least two, and sometimes three, intercostal nerves.

This vast anastomosis of the peripheral nerves in the integral parts of the body wall does not include neuron connections communicating directly with or situated in the spinal cord or communicating with the cerebral centers. Yet, such a wide sensory afferent distribution including the peripheral nerves makes it obvious why in the vast majority of cases of appendicitis the reflex involves more than one spinal nerve.

Mackenzie has on occasion found a distinct segmental nerve distribution as described by Head, but more frequently he has noted an overlapping of nerve segments. In this study, 10 per cent of the cases of appendicitis were found to involve the dorsal eleventh nerve only; in these instances, consideration of overlapping was obviously unnecessary. In the remaining 90 per cent, more than one nerve was found to be involved. In view of this extensive peripheral nerve anastomosis, aside from the other avenues of nerve distribution, it is not difficult to conceive of an overlapping of nerve segments. Sherrington's observation, confirmed by Langley, that there is an overlapping of the segmental skin fields becomes more convincing.

33. Hovelacque, A.: *Anatomie des nerfs crâniens et rachidiens et du système grand sympathique, chez l'homme*, Paris, Gaston Doin & Cie, 1927.

34. Davies, F.; Gladstone, R. J., and Stibbe, E. P.: *The Anatomy of the Intercostal Nerves*, J. Anat. 66:323, 1932.

Consideration of the Contralateral Reflex.—In 95 per cent of our cases, a contralateral reflex was elicited. On what physiologic and anatomic basis may this phenomenon be explained? At the midline of the body wall anteriorly and posteriorly there is anastomosis or median overlap between branches of the nerve fibers of the anterior and posterior rami of the spinal nerves of the right and left sides. These nerve fibers are, however, small, and their anastomosis is not extensive. Therefore, it would not be capable of transmitting nerve impulses so intense and far reaching in effect as those observed in this analysis. In visceral disease, the somatic afferent fibers mediate painful impulses from the periphery.³⁵ Experiments with animals on the conduction of painful afferent impulses in spinal nerves were performed by Ranson and Billingsley.³⁶ They stated that these impulses must pass through the gray matter and cross to the opposite side of the cord at or near the level at which they reach it. They stated also that Head showed that the same mechanism obtains with reference to protopathic sensibility.

From personal observations, Sherrington concluded that the nociceptive (algesic) impulses are conveyed headward in the spinal cord by way of the lateral columns. Each lateral column conveys such impulses from both lateral halves of the body and, somewhat preponderantly, those from the crossed half, whether these arcs be traced from the skin, the muscles or the viscera. Spiegel,³⁷ on the other hand, demonstrated in a vascular study that the conduction of afferent impulses from the peripheral vessels in the cat, particularly those which result in painful sensations, is mediated by crossed conduction pathways which are composed of a series of short relays and lie mainly in the ventral part of the lateral funiculi.

The physiologic conception of bilateral conduction in the cerebro-spinal nerves in man based on clinical evidence has been herein presented. The inference may therefore be drawn that there exist in man also crossed conduction pathways of the afferent components of the cerebro-spinal nerves.

Hypotheses Concerning Hyperalgesia in the Appendicular Reflex.—Deductions based on the various observations previously recorded herein have led to the formulation of the following hypotheses:

1. Minimal unilateral hyperalgesia in the appendicular reflex is confined to the eleventh dorsal spinal nerve on the ipsilateral side with occasional anatomic variations.

35. Kuntz, A.: *The Autonomic Nervous System*, ed. 2, Philadelphia, Lea & Febiger, 1934, p. 471.

36. Ranson, S. W., and Billingsley, P. R.: *The Conduction of Painful Afferent Impulses in the Spinal Nerves*, *Am. J. Physiol.* **40**:571, 1916.

37. Spiegel, E.: *Ueber das Wesen des Bauchschmerzes und seiner Begleiterscheinungen*, *Wien. med. Wchnschr.* **77**:379, 427 and 456, 1927; cited by Kuntz.³⁵

2. Minimal bilateral symmetric hyperalgesia of the appendicular reflex involves the dorsal eleventh spinal nerve on the ipsilateral and contralateral sides. The greater degree is usually found on the ipsilateral side. In this series, in 6 cases out of the 60 (10 per cent), only the dorsal eleventh spinal nerve was involved.

3. In maximal hyperalgesia of the appendicular reflex, two or more consecutive spinal nerves are involved, inclusive of the dorsal eleventh, asymmetrically and bilaterally, the greater intensity and radiation taking place on the ipsilateral side. Conversely, on the contralateral side there is less intensity of hyperalgesia and the radiation is less extensive—a lesser number of nerves being involved than on the ipsilateral side. There is greater spread of radiation above than below the dorsal eleventh nerve, bilaterally. This is anatomically axiomatic. The reaction in the contralateral side is proportionate to the degree of stimulation in the ipsilateral side but to a lesser degree. Comparatively, on either side the dorsal eleventh spinal nerve exhibits maximal hyperalgesia, and to a lesser degree are involved the nerves above and below this level. It is anatomically possible that the anastomosis in the peripheral nervous system may aid in the irradiation of the nerve impulses.

SUMMARY

The dorsal eleventh spinal nerve unilaterally and/or bilaterally exhibits maximal hyperalgesia and to a lesser degree are involved the nerves above and below this level.

The six points of tenderness along the course of the dorsal eleventh nerve in appendicitis are: (1) in the eleventh intercostal space, elicited by pressure of the examining fingers on the tip of the twelfth rib; (2) in the rectus abdominis muscle slightly mesial to the lateral margin and about on a level with the anterior superior spine of the ilium, and (3) the intersection of a line between these two points and the fleshy margin of the external oblique muscle (frequently located on a level with the umbilicus). There are three points on the right and three on the left side.

Hyperalgesia on the contralateral side was observed in 95 per cent of the cases of proved appendicitis.

The reaction on the contralateral side is milder, and fewer spinal nerves are involved.

This study is based on 60 cases in which the dorsal eleventh spinal nerve was involved maximally on the right side in 55 cases, or 91.7 per cent, and on the left, in 53, or 88.3 per cent.

In 10 per cent of the cases involvement was noted of the dorsal eleventh nerve only, unilaterally and/or bilaterally, while in 90 per cent,

more than one nerve was involved bilaterally. The former have been termed minimal cases and the latter maximal (table 4).

Paravertebral injection of a 2 per cent solution of procaine hydrochloride in the region of the right dorsal eleventh nerve in a case of appendicitis caused pain on the right and left sides to disappear, including that in the chest and in the back. Hyperalgesia likewise disappeared or diminished, and nausea cleared up. A diminished bilateral hyperalgesia of the tender points along the course of the dorsal eleventh spinal nerve likewise persisted.

TABLE 4.—*Typical Cases of Appendicitis with Reference to Hyperalgesia**

Location	Case 49 (Minimal)		Case 59 (Maximal)		Case 33 (Maximal)		Case 35 (Maximal)	
	Right Side	Left Side	Right Side	Left Side	Right Side	Left Side	Right Side	Left Side
Dorsal 5.....	0	0	0	0	— +	0	0	0
Dorsal 6.....	0	0	0	0	+ —	0	0	0
Dorsal 7.....	0	0	0	0	1+	0	0	0
Dorsal 8.....	0	0	0	0	1+	0	0	0
Dorsal 9.....	0	0	0	0	1+	+ —	+ —	0
Dorsal 10.....	0	0	1+	+ —	2+	+ —	+ —	+ —
Dorsal 11.....	1+	+ —	2+	1+	2+	1+	1+	+ —
Dorsal 12.....	0	0	+ —	+ —	1+	+ —	+ —	0
Lumbar 1.....	0	0	0	0	1+	+ —	0	0
Lumbar 2.....	0	0	0	0	1+	+ —	0	0
First point: Eleventh intercostal space at the tip of the twelfth rib...	1+	+ —	2+	1+	1+	+ —	2+	1+
Second point: Rectus abdominis muscle slightly mesial to the lat- eral margin and about on a level with the anterior superior spine of the ilium.....	1+	+ —	2+	1+	1+	+ —	3+	2+
Third point: Edge of the external oblique muscle.....	1+	+ —	2+	1+	1+	+ —	1+	+ —
Disease of the appendix.....	Moderate chronic appendicitis		Chronic appendicitis		Chronic appendicitis		Retrocecal gangrenous appendicitis and diffuse suppurative peritonitis	

* + — signifies very mild hyperalgesia; — +, doubtful or inconstant.

It is believed that the spread of radiation to higher nerve segments may be directly or indirectly concerned with the gastric and pyloric reflexes in appendicitis producing in addition to the diffuse or local pains reverse peristalsis or spasm of the pylorus.

The upper and lower limits of hyperalgesia, bilaterally, are recorded in tables 3 A and 3 B. Comparison of both tables reveals a greater radiation on the right side, extending from the dorsal third to the lumbar second spinal nerves, than on the left.

Retrocecal appendicitis may be differentiated from diseases of the ureter by eliciting the tender points described and noting their pre- dominance over the tender points present in ureteral diseases.³²

In several patients with appendicitis operated on by me, the appendix was not located directly under, or even in the vicinity of, the maximal point of tenderness in the abdominal wall. This is in accord with the observations of others.

There are longitudinal and transverse muscle segments in the body wall in which intersegmental anastomosis of the peripheral nerves may take place.

On the basis of the clinical evidence herein presented, it may be stated that there apparently exist in man crossed conduction pathways of the afferent components of the cerebrospinal nerves which produce a contralateral reflex.

The classification of the appendicular reflex into minimal unilateral, minimal bilateral symmetric and maximal bilateral asymmetric has been given. Hypotheses have been formulated concerning the *modus operandi* of the reflex.

Dr. E. D. Congdon, professor of anatomy at the Long Island College of Medicine, contributed the anatomic material used in dissection in these studies and gave advice; my associates at the Israel-Zion Hospital permitted the use of clinical material, and Dr. Frederick Weintraub advised in the preparation of the manuscript.

7000 Bay Parkway.

STRANGULATED FEMORAL HERNIA

GILBERT O. DEAN, M.D.

LITTLE ROCK, ARK.

Strangulation is the most frequent and most serious complication of femoral hernia. Fourteen per cent of two hundred and twenty-two femoral hernias (31 patients) were strangulated on admission of the patients to the University Hospitals, and an additional 23 per cent had been strangulated on previous occasions. Thirty-two per cent of the patients with strangulated hernias died, and 42 per cent had serious postoperative complications. However, only 1.3 per cent of the patients whose hernias were not strangulated died.

ETIOLOGIC FACTORS

The small size, the rigidity and the horizontal placement of the femoral ring (fig. 1) account for the frequency of strangulation as well as for the tendency toward early development of gangrene.

Any sudden increase in the intra-abdominal tension may cause strangulation. The most common precipitating factors in the cases at University Hospitals were heavy lifting, excessive straining, vomiting, falling, parturition, constipation and trauma to the abdomen.

Irreducibility, obstruction and inflammation of the hernial contents enhanced the development of strangulation.

The age limits were 86 and 22 years; the average age was 56 years. Strangulation was more common in women than in men and occurred more often on the left side than on the right. Femoral hernia, however, was more common on the right side.

IMPORTANT PATHOLOGIC CHANGES

A strangulated loop of bowel may become gangrenous and perforate within five hours after the symptoms begin.¹ The area of gangrene may develop as a small spot on the intestinal wall, as an encircling band at the site of constriction or as a purplish black flush involving an entire intestinal loop.

From the Department of Surgery, State University of Iowa College of Medicine.

1. Watson, L. F.: *Hernia*, ed. 2, St. Louis, C. V. Mosby Company, 1938.

Owing to the small size of the femoral ring, the hernial sac often admits only a portion of the circumference of the intestinal wall, to constitute a partial enterocoele or a hernia of Richter's type (fig. 2). In such a hernia, only the constricted antimesenteric portion of the intestinal wall tends to become gangrenous. Perforations usually occur through the antimesenteric border in either complete or partial enterocoeles.

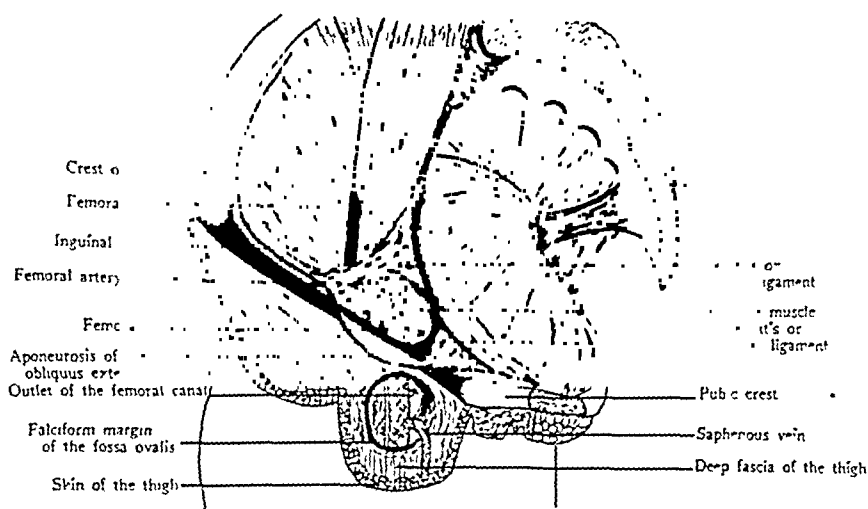


Fig. 1.—The femoral region.

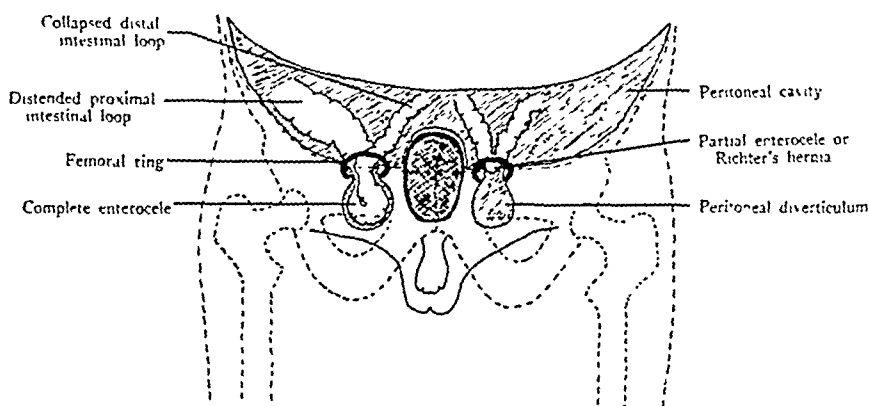


Fig. 2.—Diagram illustrating the mechanism of complete and partial enterocoele.

On rare occasions gangrene will involve a portion of the intestine which remains within the abdomen. Such a complication may be caused by extension of the thrombotic process from the vessels of the herniated intestine into the mesenteric vessels of the nonherniated intestine. A similar condition may develop if only the mesentery of the intestine becomes strangulated.

HERNIAL CONTENTS

The small intestine was the more often strangulated. In this series eighteen hernias contained loops of small intestine. These had undergone various degrees of congestion and inflammation but were still viable after being strangulated for periods varying from two hours to seven days. Six hernias contained gangrenous portions of small intestine varying in size from areas 2 cm. in diameter to entire segments 12 cm. in length. The latter six hernias had been strangulated twenty, twenty-four, sixty, seventy-two, one hundred and forty-four and two hundred and forty hours, respectively. In the last case, one of partial enterocoele, a spontaneous cutaneous fecal fistula had developed before the patient entered the hospital (fig. 3). Nine, or 29 per cent, of the

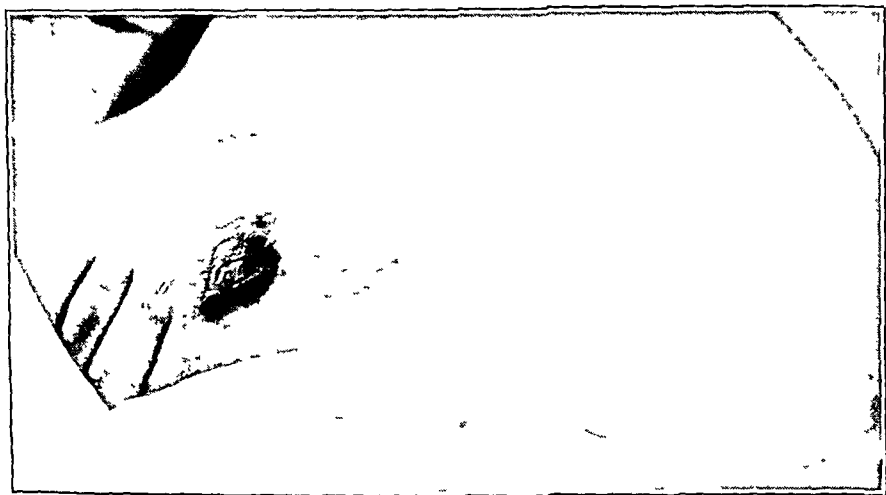


Fig. 3.—Photograph showing a spontaneous cutaneous fecal fistula which resulted from prolonged strangulation of a femoral hernia of Richter's type.

strangulated hernias presented partial enterocoeles, and three of the nine contained gangrenous small intestine.

A portion of the sigmoid colon containing a large fecalith was strangulated in one hernia for eleven hours. At operation the congested loop was viable and reducible. In this hernia the loop of the sigmoid was probably obstructed by the fecalith before strangulation ensued. Five hernias contained gangrenous omentum, and they had been strangulated for an average period of ten days. The remaining strangulated hernia contained a gangrenous epiploic appendage of sigmoid colon.

Although no similar cases have been recorded at the University Hospitals, such viscera as the urinary bladder,² the appendix, the ovary,

2. Vastola, A. R.: Strangulated Femoral Cystocoele, *Ann. Surg.* **97**:724-732 (May) 1933.

the fallopian tube, Meckel's diverticulum, the stomach and the cecum may also become strangulated in a femoral hernia.¹ In one report³ there was described an embryonic kidney which was present in a strangulated femoral hernia.

SYMPTOMS AND SIGNS

Most of the femoral hernias were recognized and observed by the patients for several years before strangulation occurred. The average period of observation in this series was five and one-half years; the longest period was twenty-five years. In 6 cases, however, the onset of strangulation was the first indication that a femoral hernia was present.

When the symptoms of strangulation occurred, the patient usually noticed that the hernial mass had become definitely irreducible, firm and tender. The mass no longer transmitted a cough impulse and had increased somewhat in size. The hernial mass was usually located on the thigh beneath the medial extremity of the inguinal ligament (fig. 4), but in 10 cases the hernia was described as lying above the inguinal ligament.

Pain was a constant symptom in the early stages of strangulation. If a portion of the bowel was strangulated, the pain was apt to be sharp and sudden in onset with exacerbations as peristalsis was stimulated. The pains tended to radiate over the abdomen as intestinal obstruction ensued. If only the omentum was involved, the pain tended to be milder, more localized and aching in character. An aching pain, however, did not preclude the possibility of strangulated intestine. The pains continued as long as peristalsis existed. The spontaneous cessation of pain was often a sign that gangrene with paralytic ileus had developed.

Nausea and vomiting invariably followed persistent obstruction of the intestinal tract. These symptoms occurred also in every patient with strangulated partial enterocele or strangulated sigmoid colon. Nausea alone developed in 3 patients with involvement of the small bowel, but the patients were all operated on within five hours. In 1 patient who was operated on within two hours nausea or vomiting did not develop. In 2 patients with strangulated omentum nausea and vomiting developed; in 3, they did not. The strangulated epiploic appendage caused nausea but no vomiting.

Obstipation and distention ensued when the entire lumen of the intestine was obstructed. If, however, the obstruction was in the upper intestine, a considerable quantity of feces and gas was often passed with or without the aid of enemas before obstipation became evident. Although diarrhea may occur with partial enterocele, it was not observed in this series.

3. Ahrens, P.: Einklemmung des Magens im Schenkelbruch, *Zentralbl. f. Chir.* 47:1345-1346, 1920.

The onset of strangulation frequently caused considerable shock and prostration. The pulse rate was usually elevated, and the temperature was often subnormal at an early stage. When shock did not develop or was overcome, the temperature became mildly elevated; it was recorded as 99.6 to 101 F. in 14 cases. When perforation of gangrenous

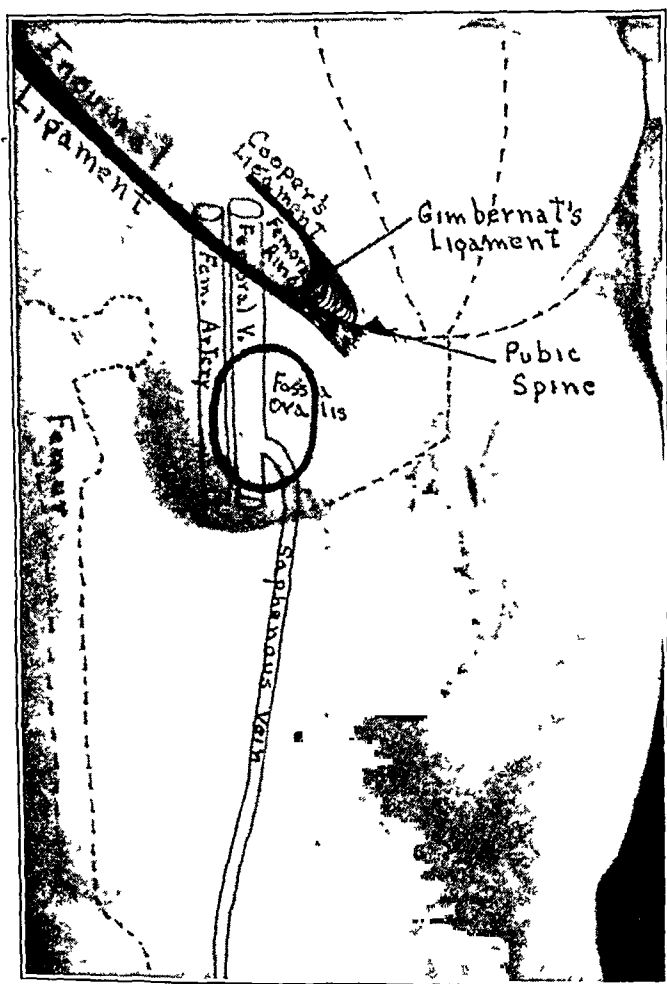


Fig. 4—Photograph of a large femoral hernia with a sketch of some of the anatomic relations.

intestine occurred or prolonged obstruction developed, ensuing peritonitis instituted a marked septic reaction.

DIAGNOSIS OF STRANGULATION

The diagnostic difficulties are emphasized by the fact that in this series the average hernia was strangulated for ninety-two hours before the patient was admitted to the University Hospitals.

In 23 of the 31 cases, strangulation was correctly diagnosed on admission. In 3, the anomaly was thought to be strangulated inguinal hernia. In 2, it was called irreducible hernia. In 2, the diagnosis was unexplained intestinal obstruction. In the remaining case, the hernia contained only omentum and was not recognized as being strangulated until the femoral region was explored. In all but the last case, however, operation was performed immediately after the patient entered the hospital.

Three conditions which may increase the diagnostic difficulties are: (1) an aberrant position of the hernial mass; (2) a lack of tenderness or pain in the femoral region; (3) total absence of a visible or palpable femoral protuberance. Difficulties are also encountered in making a diagnosis of strangulated femoral hernia in an extremely old and gravely ill patient since such a patient is often unable to give a lucid history.

The differential diagnosis includes chiefly: strangulated inguinal hernia, thrombophlebitis of the great saphenous vein and femoral lymphadenitis. Rarer conditions are: strangulated lipoma, psoas abscess, distention of the iliac bursa, femoral aneurysm, hydatid cyst, hernia of one of the adductor muscles and strangulated obturator hernia.

TREATMENT

Immediate operation is the treatment of choice for strangulation of a femoral hernia. Attempts to reduce the strangulated viscera by taxis not only prolong the hazardous delay but add the following possible dangers: reduction en masse without relief of the strangulation; displacement of the hernial mass with consequent confusion of the clinical picture; rupture of the strangulated intestine whether viable or gangrenous; replacement of gangrenous or perforated intestine within the peritoneal cavity; the occurrence of intestinal hemorrhage because of contusion, laceration or ulceration; incomplete reduction with a portion of the strangulated viscera remaining in the sac; the development of paralytic ileus. Furthermore, successful reduction of a hernia by taxis is often only a temporary palliative measure, offering no security against recurrence of the strangulation.

In addition to the preoperative and postoperative care and the repair of the hernial defect, the surgeon is confronted with one or more of four major problems: (1) choice of a surgical approach; (2) selection of the method of reducing the strangulated viscera; (3) accurate examination of the viscera; (4) treatment of gangrenous viscera.

Surgical Approach.—There are three possible surgical approaches to a strangulated femoral hernia: (1) through the femoral region; (2) through the inguinal region; (3) through combined lower abdominal and femoral incisions.

An approach from below the inguinal ligament can be carried out rapidly with the least amount of tissue destruction and with the least shock to the patient. The small operative field encourages the use of local anesthesia. The femoral approach, however, offers only the small femoral ring as an exploratory opening through which the strangulated viscera must be delivered for examination and treatment and through which the abdominal cavity may be investigated for additional pathologic changes. Furthermore, the reduction of congested and inflamed viscera through the femoral canal from below is often difficult and dangerous. An attempt to enlarge the femoral ring from below may injure the urinary bladder or sever an aberrant obturator artery.

The inguinal approach can be utilized with a small amount of tissue destruction and shock to the patient, although the procedure is more time consuming than the femoral approach. The floor of the inguinal canal is necessarily opened and offers a fairly large introitus for examining and treating the strangulated viscera and for exploring the abdominal cavity. The inguinal approach offers an excellent exposure of the femoral ring, and any manipulations necessary for reducing the viscera or enlarging the ring can be carried out with all important structures under satisfactory vision. The inguinal incision can also be extended downward to expose the hernial mass from below the inguinal ligament; this facilitates the liberation and reduction of an adherent sac. Local anesthesia can be utilized in most cases, but if general anesthesia is required, a gas anesthetic will give sufficient relaxation. The disadvantage of the inguinal approach is that the floor of the inguinal canal is weakened and must be carefully repaired to prevent later development of an inguinal hernia. However, this exposure of the femoral region enables the surgeon to obtain a higher ligation of the femoral sac and a more adequate approximation of the fascial structures for the repair of the femoral defect.

The combined abdominal and femoral approach consists of two incisions; the first may be either a vertical rectus or a transverse abdominal incision, and the second is the usual femoral incision. Either of the two abdominal incisions offers good exposure of the abdominal cavity and allows the surgeon ample space for examining and treating the involved viscera after their reduction is accomplished. The combined approach is frequently preferred when the strangulation has persisted for a long period, when extensive pathologic changes have occurred in the hernia or when it becomes necessary to explore the abdominal cavity for elusive loops of diseased intestine or strangulated omentum. The disadvantages are that it is time consuming, causes much destruction of tissue, requires general or spinal anesthesia and may cause considerable shock. Since the combined approach is a procedure of

greater magnitude and is utilized for the more serious cases, it is followed by more postoperative complications than either the femoral or the inguinal approach.

In this series the femoral approach alone was used nineteen times, the inguinal approach six times, and the combined abdominal and femoral approach six times.

Reduction of the Strangulated Viscera.—Strangulated bowel is often bound to the hernial sac by dense fibrous adhesions which must be removed by sharp dissection. Since the tissues are usually swollen and friable, great care must be exerted not to damage the bowel during the process of separating it from the sac.

After the adhesions are removed, the strangulated viscera can usually be reduced by light pressure from below or by gentle traction on the contiguous structures within the abdomen. A combination of the two procedures is more effective than either pressure or traction alone.

Sometimes the reduction is impossible unless the constricting femoral ring and the neck of the sac are enlarged. The best method of enlarging these structures is to cut medially into the lacunar or Gimbernat ligament. Still greater relaxation of the femoral ring can be obtained by cutting through the inguinal ligament anteriorly, but the latter procedure results in a higher percentage of recurrent hernias despite careful attempts to repair all structures. The recurrence rate is not increased by cutting the lacunar ligament if the incised structures are repaired. In this series the lacunar ligament was cut five times with no recurrence of hernia. The inguinal ligament was incised in 2 cases, in 1 of which hernia later recurred.

Examination of the Strangulated Viscera.—After the constricting mechanism is released, the viscera should be withdrawn from the wound and examined for (1) pulsation in the arteries, (2) bleeding from denuded or incised areas and (3) disappearance of the blue-black or purplish color changes. If these signs of returning circulation do not appear immediately, the viscera should be covered with warm moist compresses and inspected at five to ten minute intervals. During the period of waiting the operator should be certain that all points of constriction are completely freed and that no volvulus has occurred. A careful search for minute perforations should be made. The mesenteric vessels should also be examined for possible thrombosis beyond the area of strangulation.

Treatment of Gangrenous Viscera.—The successful treatment of a gangrenous intestine consists of two steps: the removal of the gangrenous area and the reestablishment of the intestinal continuity.

A small necrotic area with or without perforation may be treated by inversion into the intestinal wall. The healthy serosa and a tag of

omentum are then sutured over the site of the inversion. A necrotic encircling band may be similarly inverted to produce partial intussusception of the gangrenous material, which subsequently sloughs into the intestinal lumen.

When the gangrenous involvement is too extensive for inversion, the procedure of choice is resection and primary anastomosis. The other alternative is the establishment of an enterostomy with a resultant fecal fistula or artificial anus. Resection and primary anastomosis are imperative if the gangrenous area is high in the intestinal tract, and they are preferable whenever the small intestine is involved unless the patient's general condition prohibits any procedures except simple exteriorization of the diseased loops. Such conditions as extreme intestinal dilatation, generalized peritonitis or gangrenous involvement of several feet of intestine may prevent successful resection and anastomosis. Many surgeons reserve enterostomy for treating gangrenous areas in the descending and the sigmoid colon.

CAUSES OF DEATH

The mortality rate was 83 per cent among the patients with gangrenous intestine; 50 per cent died because of generalized peritonitis and 33 per cent because of wound infection with septicemia or respiratory complications. The mortality rate among patients without gangrenous intestine was 16 per cent; 2 patients died from cardiac decompensation and 1 from generalized peritonitis due to laceration of a loop of bowel.

The hernias of the patients who died after operation had been strangulated for an average period of eighty-five hours, whereas those of the patients who recovered had been strangulated for an average period of thirty-seven hours. The average age was 66 years for the patients who died and 52 years for those who recovered.

When strangulation occurs, the mortality rate is increased by these factors: (1) a long period of strangulation; (2) gangrene of the strangulated bowel; (3) adherence of the strangulated bowel to the hernial sac; (4) attempts at reduction by taxis; (5) advanced age of the patients.

RECURRENCES

A follow-up study of all the patients who were treated for femoral hernia revealed that in 23 per cent of those in whom strangulation was present at the time of operation the hernia recurred whereas recurrences developed in only 12 per cent of those in whom hernia had been uncomplicated. One patient had recurrence of hernia and strangulation one year after the first strangulated hernia was repaired, and died as a result of the second strangulation.

SUMMARY AND CONCLUSIONS

Since the mortality rate was 32 per cent and the recurrence rate was 23 per cent, only 45 per cent of the strangulated femoral hernias were cured by the operative procedures. In contrast, 88 per cent of the non-strangulated femoral hernias were cured by operation. The occurrence of strangulation evidently caused a 50 per cent decrease in the chances of curing the hernia by operation. It is imperative, therefore, if the surgeon wishes to offer patients with femoral hernia better than a 70 per cent chance of remaining alive and better than a 50 per cent chance of being cured that he fulfil the following demands: (1) Suspect strangulation of every femoral hernia; (2) operate on every strangulated femoral hernia immediately after the diagnosis is made; (3) avoid reduction by taxis; (4) carefully select the operative approach which allows adequate exposure for reduction, examination and treatment of the strangulated viscera; (5) preferably use inversion or primary resection for all areas of gangrenous intestine; (6) reserve the procedure of enterostomy for gangrenous portions of the lower part of the colon and for patients who cannot tolerate anything more than simple exteriorization of the diseased loops of intestine; (7) perform early repair of every femoral hernia.

701 Main Street.

STIMULATION OF THE CELIAC PLEXUS IN THE DOG

I. CARDIOVASCULAR AND RESPIRATORY EFFECTS

S. J. MARTIN, M.D.

C. L. BURSTEIN, M.D.

AND

E. A. ROVENSTINE, M.D.

NEW YORK

The response to stimulation of the abdominal viscera and the mechanism involved has been a subject of unusual interest and considerable controversy for laboratory and clinical investigators for a long time. Many years ago, Mayer and Pribram¹ and, later, Brodie and Russell² observed a rise in the arterial blood pressure with an increase or a decrease in the heart rate following distention of the stomach. Davis and co-workers³ and Schrager and Ivy⁴ in still later reports showed that stretching of the biliary and cystic ducts produced apnea and a variable change in the blood pressure as well as in the heart rate. It was believed that stimulation of the vagus and right splanchnic nerves was responsible for the phenomena observed. Luckhardt and associates⁵ noted the appearance of apnea and an immediate fall in the blood pressure following manipulation and traction on the gastrohepatic ligament. While they explained the respiratory effects on the basis of vagal stimulation, they expressed the belief that the circulatory changes were due to mechanical rather than to vasomotor influences. Others showed that traction on the gastric and duodenal arteries is regularly followed by a fall in the blood pressure and/or a reflex vocal cord adduction with laryngospasm or apnea. Recently, Crowley⁶ stated in a preliminary report that distention of the small intestine generally produces apnea and an immediate rise in the blood pressure. All of these studies were concerned solely with the stimulation of the viscera

From the Division of Surgery, Department of Anesthesia, New York University College of Medicine.

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2. Brodie, T. G., and Russell, A. E.: *J. Physiol.* **26**:92, 1900.

3. Davis, L. E.; Hart, J. T., and Crain, R. C.: *Surg., Gynec. & Obst.* **48**: 647, 1929.

4. Schrager, V. L., and Ivy, A. C.: *Surg., Gynec. & Obst.* **47**:1, 1928.

5. Luckhardt, A. B.; Alpert, R., and Smith, S.: *Science* **76**:545, 1932.

6. Crowley, R. T.: *Am. J. Physiol.* **133**:P 253, 1941.

per se and failed to establish the presence of a predominant pattern response following stimulation of the viscera of the upper part of the abdomen.

Since it is established that the viscera of the upper part of the abdomen possess a dual autonomic innervation and that both the vagal and the sympathetic branches contain afferent⁷ as well as efferent fibers, a more direct approach to the problem of visceral stimulation is gained by studying the nervous structures concerned. Such studies, which are few, have revealed inadequate and conflicting data. Auer and Meltzer⁸ observed a fall in the blood pressure after stimulation of the splanchnic nerve in dogs and rabbits and concluded that the abdominal viscera have a reflex depressor innervation. This phenomenon was observed also in dogs by Burton-Opitz.⁹ In the cat, an elevation in the blood pressure followed stimulation of the splanchnic nerve.¹⁰ Laignel-Lavastine¹¹ observed an elevation of the arterial blood pressure and vasoconstriction of the spleen and the intestine following stimulation of the celiac ganglions in dogs. From the anatomic point of view, Ingersoll established the fact that stimulation of the abdominal viscera produces definite cytologic changes in the celiac ganglion cells.¹²

With the exception of the studies of Laignel-Lavastine and Ingersoll and the preliminary investigations in this laboratory,¹³ no other significant report has been found with reference to stimulation of the celiac plexus. Since this plexus with its accompanying splanchnic and abdominal vagal nerves is admittedly the point of convergence for stimuli coming from the viscera of the upper part of the abdomen, it seemed advisable to study the responses to stimulation of these nervous structures rather than of the viscera themselves. Accordingly, it was made the subject of this investigation, and the observed cardiovascular and respiratory effects are hereinafter reported.

PROCEDURE

Twenty-nine dogs ranging from 9 to 18 Kg. in body weight were used. Premedication with morphine sulfate (2.5 to 5 mg.) and atropine sulfate or

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8. Auer, J., and Meltzer, S. J.: (a) *Am. J. Physiol.* **31**:21, 1912; (b) *Zentralbl. f. Physiol.* **26**:1316, 1913.

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10. (a) Davis, L. E.: *Am. J. Physiol.* **60**:560, 1922. (b) Sollmann, T., and Pilcher, J. D.: *ibid.* **30**:369, 1912. (c) Davis.^{7b}

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scopolamine hydrobromide (0.05 to 0.1 mg. per kilogram of body weight) was given subcutaneously one hour before anesthesia was induced. Anesthesia was maintained for one to three hours with ether or cyclopropane given by the closed carbon dioxide absorption technic. An endotracheal airway with inflatable cuff was always used. In a few instances, chloralosane^{13a} (80 to 90 mg. per kilogram) was employed. Caution was exercised to keep anesthesia uniformly at the second plane of the surgical stage.

Through a left dorsolateral abdominal incision, the celiac plexus was exposed, and the left splanchnic and right abdominal vagal nerves approaching it were isolated from the surrounding tissue. Narrow ribbons of cloth, moistened with physiologic solution of sodium chloride were placed underneath these structures to facilitate handling. The identity of the separate nervous elements was verified by autopsy of all animals used in this investigation.

Carotid arterial tensions and pulse pressures were kymographically recorded with the aid of a mercury manometer; venous pressures were read directly from a calibrated glass tube inserted into the femoral vein. Serial electrocardiograms of lead II with the dogs on their right side were also obtained. Respiratory changes were recorded by a kymograph with the use of a tambour-lever arrangement and a pneumograph placed around the lower portion of the thorax.

Preliminary studies¹³ consisting of pulling the stomach, the gallbladder or the duodenum or manually pinching the celiac plexus resulted in a variable response largely due to the lack of control of stimuli employed. It was therefore considered advisable to employ forms of stimulation that could be more satisfactorily controlled. Accordingly, throughout this study the methods of stimulation used were: (1) to apply constant and even tension on the ribbons of cloth placed under the celiac plexus, the left splanchnic or right abdominal vagal nerves; (2) to employ constant faradic stimulation with the aid of a platinum electrode for an average of twenty to thirty seconds to these structures. These were regarded as moderate or strong stimuli. The cardiovascular and respiratory changes obtained were compared with control observations before and after stimulation.

RESULTS

More than four hundred experimental observations have been made of the cardiovascular and respiratory changes resulting from the application of various stimuli to the celiac plexus, the intact and proximal end of the cut left splanchnic nerve and the right abdominal vagus nerve. These observations have been analyzed and the findings grouped in the following categories:

Cardiovascular Changes.—(a) Arterial and Pulse Pressures: The effects on the mean arterial and pulse pressures after mechanical and faradic stimulation of these nervous structures are briefly summarized in table 1. It will be seen that although there was some variability in the results, a distinct and predominant pattern response existed following stimulation of the celiac plexus and the intact and proximal

^{13a}. Chloralosane is a preparation of chloralose (a compound of chloral hydrate and dextrose) which has been purified of parachloralose and other impurities.

end of the cut splanchnic nerve. This pattern was characterized by a rise in the mean arterial blood pressure and a decrease in the pulse pressure. It was produced more consistently after faradic than after mechanical stimulation, and, lastly, it was practically absent on stimulation of the intact or proximal end of the cut abdominal vagus nerve (fig. 1). The pattern response remained essentially unaltered following stimulation of the celiac plexus after both vagi were sectioned but was markedly diminished when stimulation followed section of the left splanchnic nerve. The most consistent elevation of the mean arterial pressure and decrease in the pulse pressure were noted after stimulation during anesthesia induced with ether. The absence of pressure changes

TABLE 1.—*Variation in the Circulatory Effects Following Stimulation of the Celiac Ganglion, the Splanchnic and Abdominal Vagal Nerves in Dogs*

Structure Stimulated	Type of Stimulation	Mean Arterial Blood Pressure Changes				Pulse Pressure Changes				Venous Pressure Changes			
		Number of Observations	Rise, per Cent	Fall, per Cent	No Effect, per Cent	Number of Observations	Rise, per Cent	Fall, per Cent	No Effect, per Cent	Number of Observations	Rise, per Cent	Fall, per Cent	No Effect, per Cent
Left celiac ganglion	Ligature tension	77	59	18	22	77	3	61	36	20	55	15	30
	Faradic	39	77	5	18	29	0	69	31	7	86	0	14
Left splanchnic nerve	Ligature tension	48	48	17	35	33	6	36	58	13	54	0	46
	Faradic	34	79	6	15	30	0	73	27	8	63	0	37
Right abdominal vagus nerve	Ligature tension	30	4	13	83	23	0	22	78	5	60	0	40
	Faradic	25	20	12	68	20	5	0	95	4	50	0	50

in a few cases, noted in the table, may be accounted for by the use of inadequate mechanical and faradic stimuli.

The rise in the mean arterial blood pressure ranged from 10 to 90 mm. of mercury (average, 40 mm. of mercury), depending on the type of stimulus employed. It was greater following stimulation of the splanchnic nerve than after stimulation of the celiac plexus and was minimal or negligible when the vagus nerve was stimulated. In over 70 per cent of the observations, the rise in the systolic blood pressure was proportionately less than in the diastolic, with a resulting decrease in the pulse pressure (fig. 1). The decrease in the pulse pressure varied from 4 to 24 mm. of mercury and was followed by a gradual return to normal or, more commonly, by a temporary increase in the pulse pressure. When a fall in the arterial blood pressure occurred (average, 18 mm. of mercury), there was usually an accompanying decrease in the pulse pressure. The pulse pressure was initi-

ally increased in 5 cases, in 3 of which it accompanied a fall in the mean arterial blood pressure.

In all instances, the changes in the mean arterial blood and pulse pressures started abruptly on stimulation and disappeared in one to ten minutes. Occasionally, the initial rise in arterial blood pressure was followed by a slower secondary rise or a compensatory fall.

(b) Venous Pressure: Venous pressure readings in 57 instances made during and after mechanical and faradic stimulation of the various

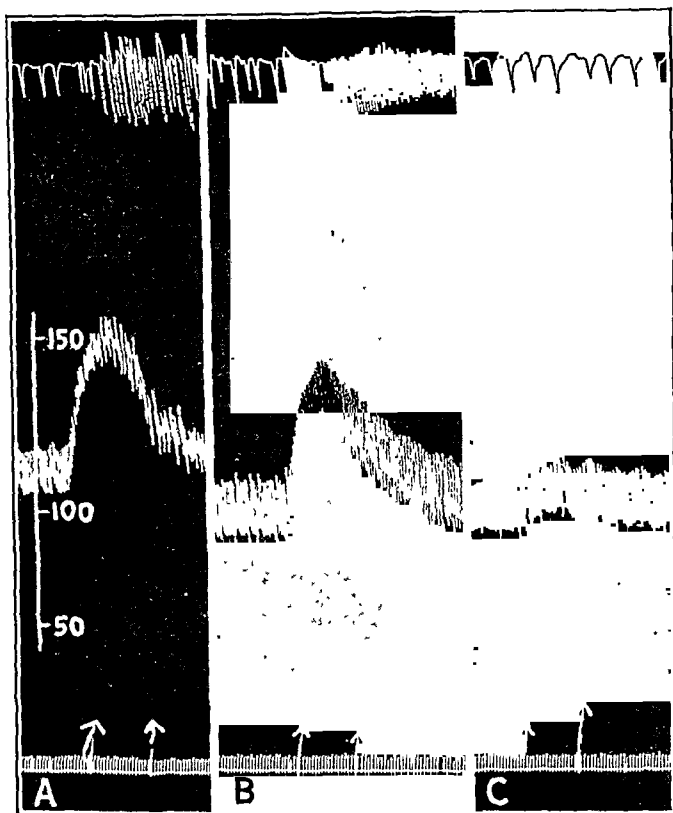


Fig. 1.—Apnea, a rise in the mean arterial pressure and a decrease in the pulse pressure are noted following faradic stimulation of the celiac plexus (A) and the proximal end of the cut left splanchnic nerve (B) in an etherized dog. Relatively slight effects follow stimulation of the central end of the cut abdominal vagus nerve (C). The upper, middle and lower tracings represent respiration, blood pressure and time in second intervals, respectively; the period of stimulation is noted between arrows.

nervous structures showed that if a change occurred, it was usually a rise (table 1). This elevation followed the arterial pressure rise and in all instances was gradual in onset and ranged in magnitude from 8 to 60 mm. of solution of sodium chloride, depending on the type of stimulus employed. Normal levels were reached in one to five minutes.

In 2 instances, a fall in venous pressure followed a decrease in mean arterial blood pressure. In a few cases in which there was no change in venous pressure, there was no variation in arterial pressure on stimulation.

(c) Electrocardiogram: In 5 dogs, eighty-three serial electrocardiograms of lead II were taken before, during and after mechanical and faradic stimulation of the various nervous structures. The following significant changes were noted accompanying the elevation in the mean arterial and venous pressures and the decrease in the pulse pressure: The sinus rate was increased (14 to 56 beats per minute), depending on the strength of the stimulus, whenever the celiac plexus or the left splanchnic nerve was stimulated. However, with regard to the abdominal vagus nerve, marked variability in the response was noted. The

TABLE 2.—*Variation in the Respiratory Effects Following Stimulation of the Celiac Ganglion, the Splanchnic and Abdominal Vagal Nerves in Dogs*

Structure Stimulated	Type of Stimulation	Number of Observations	Initial Apnea Followed by Polypnea, per Cent	Initial Apnea Followed by Gradual Return to Normal, per Cent	Initial Polypnea with Gradual Return to Normal, per Cent	Temporary Decrease in Rate and Amplitude, per Cent	No Effects, per Cent
Left celiac ganglion	Ligature tension	77	17	48	5	16	14
	Faradic	36	17	50	0	17	16
Left splanchnic nerve	Ligature tension	41	27	39	10	10	14
	Faradic	29	28	38	0	17	17
Right abdominal vagus nerve	Ligature tension	25	8	24	4	8	56
	Faradic	22	9	18	0	9	64

sinus tachycardia was accompanied by a regular rhythm as a rule, and a decrease in the P-R interval, an occasional slight decrease in the QRS time, decrease in the height of the P and R waves, infrequent elevation of the S-T segment and an inversion, decrease or increase in the height of the T wave. Less often, showers of auricular extrasystoles with short runs of auricular flutter occurred. Rarely, there was a slowing of the sinus rate. There were no premature ventricular beats or disturbances in bundle branch conduction. In all instances, the electrocardiographic variations disappeared shortly after cessation of stimulation of the nervous structure.

Respiratory Changes.—(a) Normal Respiration: Table 2 summarizes the more significant respiratory effects seen after the stimulation of the celiac plexus, the left splanchnic nerve and the right abdominal vagus nerve. It can readily be seen that while such effects were variable, apnea predominantly followed mechanical or faradic stimulation of the celiac plexus and the splanchnic nerve. Apnea was followed by

polypnea (fifty-six to one hundred and twenty minutes) or, more generally, by a gradual increase in rate and amplitude of respiration to the control level. However, stimulation of the abdominal vagus nerve resulted in no change in respirations or, less commonly, in apnea followed by a gradual return to normal rate and amplitude (fig. 1). The appearance of apnea followed by polypnea or a gradual return to normal respiration was not prevented by stimulation of the celiac plexus

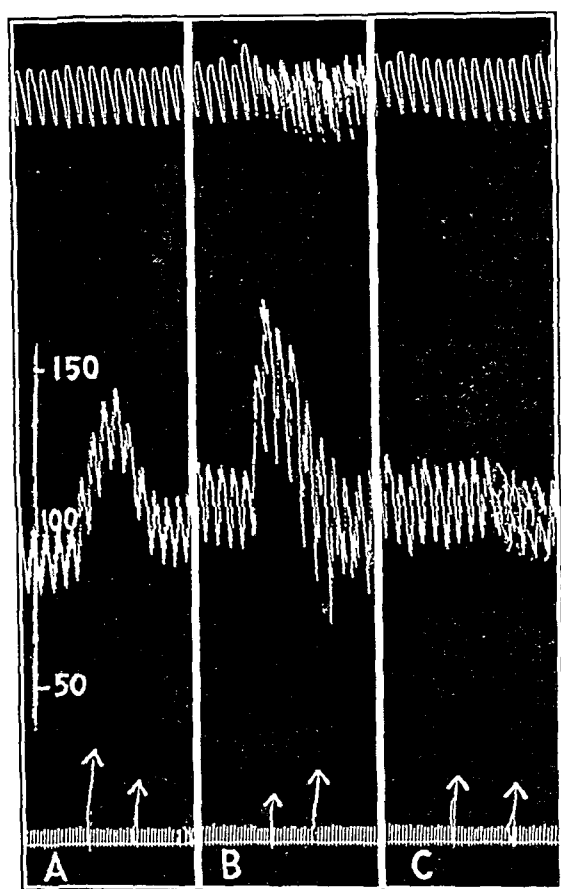


Fig. 2.—During respirations controlled to obviate respiratory changes, the rise in the mean arterial pressure and the fall in the pulse pressure still occur following faradic stimulation of the celiac plexus (A) and the cut left splanchnic nerve (B). The upper tracing denotes controlled respiration.

after the vagi were sectioned; however, after section of the splanchnic nerve, changes in respiration occurred less often.

The periods of apnea appeared abruptly on stimulation and continued for four to thirty seconds generally in the inspiratory position of the chest. Polypnea, appearing after the apneic periods or initially on stimulation, was characterized also by a marked increase in the

amplitude of respiration. Polypnea was more common and more marked following stimulation of the splanchnic nerve than of the celiac plexus. Rarely, a bizarre pattern of respiration consisting of intermittent and marked changes in both rate and amplitude was noted after stimulation. All respiratory changes disappeared in one to three minutes following cessation of stimulation.

Respiratory effects following stimulation of the nervous structures were more consistent during anesthesia induced with ether and least so when chloralose was the anesthetic employed. The absence of respiratory changes was associated with no changes in the circulation because of the inadequate stimulus used.

(b) *Controlled Respiration*: Since the predominant apneic interval was found to accompany the characteristic cardiovascular changes on stimulation, controlled respiration by means of a respiratory pump was employed to determine the relation between respiratory and circulatory effects. Seventeen observations made while stimulating the celiac plexus and/or the left splanchnic nerve during controlled respiration revealed a rise in mean arterial blood pressure, although this was not so marked as that obtained during normal respiration (fig. 2); occasionally a fall in pressure was noted. There was, however, no appreciable effect on the decrease in the pulse pressure or the rise in the venous pressure.

COMMENT

In the literature already cited, there is no agreement as to the effects from stimulation of the viscera of the upper part of the abdomen or of the splanchnic nerve. Our data indicate that a predominant pattern response, characterized by a rise in the mean arterial and venous pressures, a decrease in the pulse pressure, sinus tachycardia and apnea followed by polypnea, can be elicited following mechanical or faradic stimulation of the celiac plexus in the dog. Attention was directed to the plexus and its associated splanchnic and vagal nerves because it is regarded as the region common to most, if not all, of the innervation of the viscera of the upper part of the abdomen.

Consideration of the mechanism concerned with the appearance of this response on stimulation of the celiac plexus has been reserved for a later study.¹⁴ However, it seems from some of the data herein reported that afferent reflex stimulation of the sympathetic system may predominate. This is suggested, in part, by the fact that the cardiovascular and respiratory changes following stimulation of the celiac plexus were not influenced by severing the vagi but were markedly

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diminished after stimulation following section of the left splanchnic nerve. The afferent reflex pathway in the splanchnic nerve is apparently more significant in producing such reflex changes than that in the right abdominal vagus nerve. These findings do not substantiate Luckhardt's⁵ contention that respiratory changes are due essentially to the stimulation of the vagus nerve and that the cardiovascular effects are dependent on mechanical rather than vasomotor influences following traction of the visceral structures. That associated apnea and/or polypnea are not fundamentally responsible for the appearance of the usual vascular response is borne out by the fact that a rise in the blood pressure with a decrease in the pulse pressure was still noted when the celiac plexus was stimulated during controlled respiration.

Notwithstanding the appearance of a predominant pattern response following stimulation of the celiac plexus, it must be emphasized that variations in the results were found. While these were few in number, they are significant and are believed to be due to one or more of the following factors: (1) the type and the strength of stimulus; (2) the anesthetic agent; (3) the depth of anesthesia, and (4) species and individual variations. Preliminary studies revealed that manual pinching of the celiac plexus produces no consistent effects on the circulatory system. The use of ligature tension on the nervous structures or faradic stimulation elicited more uniform findings. The data show that weak stimulation of these types commonly produces a fall instead of a rise in the blood pressure. However, moderate or strong stimuli consistently gave rise to an elevation in the blood pressure. This phenomenon may be explained, in part, by the presence of pressor and depressor fibers requiring a weak or a strong threshold stimulus, respectively. Such an explanation has been advanced by Auer and Meltzer^{8a} for the splanchnic afferent nerves and by Hunt¹⁵ and Ranson and Billingsley¹⁶ for the somatic afferent fibers.

The anesthetic agent employed is significant in the uniformity of response obtained. The findings obtained were most consistent during anesthesia induced with ether and less consistent when cyclopropane and especially chloralose were used. It is difficult to account for such observations except to refer to the effects claimed for these agents on the sympathetic¹⁷ or parasympathetic¹⁸ divisions of the autonomic nervous system. As emphasized by Meek,¹⁹ the cardiac arrhythmias

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19. Meek, W. J.: *Physiol. Rev.* **21**:324, 1941.

noted also may be due to the anesthetic agent employed; according to Rehn,²⁰ they may result from surgical manipulation.

The influence of the degree of narcosis was eliminated in this study since all animals were carefully maintained in the second plane of the surgical stage of anesthesia. However, the subsequent investigation¹⁴ will point out the significant role of changes in the depth of anesthesia.

The possibility that species or individual differences are responsible for the variations noted has been emphasized. Davis^{10a} suggested that the connections of visceral afferent nerves (splanchnic) with the vasomotor center was radically different in the dog and in the cat. The data reported in our study apply for the dog only. Individual animal variation to constant stimuli has been noted not only in different dogs but in the same animal at different times. Evanescent and intermittent changes in the threshold values for stimulation in the viscera are probable even though experimental procedures may otherwise be rigidly controlled.

SUMMARY

The celiac plexus, the intact and cut left splanchnic nerve and the right abdominal vagal nerve were stimulated in the anesthetized dog with mechanical and faradic stimulation.

It was found that a predominant cardiovascular and respiratory response resulted from such stimulation which was characterized by a rise in the mean arterial pressure, a decrease in the pulse pressure, a rise in the venous pressure, sinus tachycardia and other electrocardiographic changes and inspiratory apnea followed by polypnea or a gradual return to normal respiration.

The pattern response remained essentially unchanged after stimulation of the celiac plexus after the vagus was sectioned; however, it was significantly altered after section of the splanchnic nerve.

Deviations from the pattern response are discussed in the light of various factors, such as the type and the strength of stimulation, the anesthetic agent, the depth of anesthesia and species and animal variations.

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MESENCEPHALIC TRACTOTOMY

A METHOD FOR THE RELIEF OF UNILATERAL INTRACTABLE PAIN

A. EARL WALKER, M.D.

CHICAGO

Although many neurosurgical procedures have been suggested for the treatment of intractable pain, chordotomy is still the most satisfactory method for the relief of pain in the lower extremities, the abdomen and the thorax. It is not safe when performed in the rostral cervical segments for intractable pain in the upper extremities, owing to the danger of respiratory failure. To avoid this complication posterior rhizotomy has been suggested, but this is undesirable since the upper extremity then becomes anesthetic and useless. This procedure is of more value for the relief of severe pain in the neck. For pain in the arm, the neck and the face, a combination of section of the fifth and ninth cranial nerves and posterior cervical rhizotomy becomes a formidable procedure, especially in a patient who is already debilitated. In such cases Dogliotti¹ suggested section of the lemniscus lateralis in the rostral part of the pons and carried out this procedure in 4 patients. Unfortunately, he has never published his case reports.

From neuroanatomic studies of the spinothalamic and secondary trigeminal pathways,² it appears that an equally effective and simpler section of the entire pain fibers from one half of the body including the face may be carried out in the mesencephalon. It has several advantages over Dogliotti's procedure: 1. The site of operation may be reached without retraction of the cerebellum such as is necessary to reach the upper portion of the pons. 2. The incision is made a considerable distance from the superior cerebellar artery and the fourth cranial nerve. 3. It may be carried deeply into the brain stem without damaging such structures as the brachium conjunctivum, which lie immediately below the pain fibers in the upper part of the pons. 4. The landmarks are clearer. It does not seem to have any disadvantages which are not possessed by the other procedure.

In man, the pain pathways from the lower extremities, the abdomen, the thorax and the upper extremities lie on the surface of the mesencephalon

From the Division of Neurological Surgery, University of Chicago.

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2. Walker, A. E.: The Spinothalamic Tract in Man, *Arch. Neurol. & Psychiat.* **43**:284-298 (Feb.) 1940.

just above the lateral sulcus scattered throughout the extent of the lateral lemniscus. In the monkey, the secondary pain fibers from the trigeminal nucleus lie at the level of the lateral sulcus along the lateral margin of the medial lemniscus, and it seems likely that their localization is somewhat similar in the human being. Hence it seemed that a complete section of the pain fibers from the opposite side of the body could be carried out at this level. The procedure was performed on several macaques. In these animals, owing to the preservation of tactile sensibility, hemianalgesia could not be clearly demonstrated. Subsequently the procedure was carried out on 2 patients, both having intractable pain.

REPORT OF CASES

CASE 1.—Left mesencephalic tractotomy was performed on a patient with intractable pain on the right side associated with a thalamic syndrome. Right hemianalgesia resulted. Death occurred in twenty-four hours due to cerebral edema. Autopsy was performed.

E. E., an unemployed married Negro laborer 33 years old, was referred by Dr. George B. Hassin and hospitalized on Aug. 4, 1939. He complained of severe pain on the entire right side of body, including the face, and weakness of the right extremities.

Except for a momentary dizzy spell in September 1938, he was well until March 3, 1939, when suddenly he suffered complete right sensory and motor hemiplegia with aphasia. He became irritable, easily perturbed and angered. His wife stated that it was almost impossible to live with him.

From the time of the stroke he suffered severe pain in the entire right side of the body. It felt as if it were "on fire," "drawing up," "gripping," "constricted." Even the weight of bedclothes on the right extremities was unbearable. This pain became worse as the paralysis regressed. It was so severe that he could not put his foot on the floor. The pain or dysesthesia was constantly present but touching the right extremities or rubbing one's hand over them caused intolerable burning.

The patient's personal, familial and systemic histories were essentially irrelevant. He was disoriented in time, place and person, although he knew his own name and recognized his wife.

The cranial nerves were normal except for the following findings: Sensation over the left side of the face was normal. On the right side the threshold for touch was markedly heightened so that even with a 20 Gm. per millimeter Frey hair only about 50 per cent of the stimuli were appreciated. A 1 Gm. per millimeter hair, about the normal threshold stimuli, was not felt at all on the right side, although on the left side about 50 per cent of the trials were appreciated. Pricking the right side of the face caused a peculiar burning sensation with diffuse radiation, even to the right arm and leg. With a 0.5 Gm. Frey pin, seven to ten sticks were required to initiate diffuse burning dysesthesia, which would then last for one to several minutes, gradually becoming more severe and radiating to adjacent areas, at times to the ipsilateral arm and leg. With a 1 Gm. Frey pin about three pricks were required to produce the burning, but with a 2 Gm. pin, a single prick would bring it on. When an 8 Gm. Frey pin

and a tube of ice water were applied to the right side of the face, the patient, blindfolded, was unable to differentiate the two stimuli; both gave rise to burning dysesthesia. Usually irrespective of the type of stimuli, the patient said he was pricked. There was no deviation of the jaw on opening the mouth. The right corneal reflex was diminished. There was a slight weakness in the right lower part of the face, especially pronounced in emotional movements. Hearing was slightly impaired in the right ear for all tones and in the left ear for high tones. Caloric examinations were not made. The right sternocleidomastoid muscle did not contract as well as the left. The right arm was markedly paretic at the shoulder and the elbow and practically paralyzed at the wrist and the finger joints. The right leg was weak, and the ankle and toes could barely be moved. There was marked spasticity in both the right arm and the right leg with lively tendon reflexes and a sustained right ankle clonus. The plantar response was, however, flexor. The abdominal reflexes were absent on both sides. There were no involuntary movements of the right extremities.

Sensation in the right arm and the right leg and the right side of the abdomen was much the same as on the right side of the face. The patient was unable to distinguish between the prick of an 8 Gm. Frey pin and the touch of a tube of ice water, and both caused burning dysesthesia. Occasionally, the pin was said to stick. Even the application of a vibrating tuning fork gave rise to the burning pain. Fine touch was not appreciated on the right arm or the right leg. Position sense was entirely lost. The patient could not even tell which finger or toe was moved. There was complete right astereognosis. With his eyes covered, the patient confused the observer's hand for his own right hand, claiming after feeling the examiner's hand with his left hand that it was his own. He had, however, no difficulty in finding his right hand in space, and he had no illusions of movement of the paretic limbs. He was able to walk in a hemiplegic fashion with the aid of a cane.

Laboratory examinations, including urinalysis, blood studies, studies of sugar tolerance curves, spinal fluid studies and roentgenograms of the skull and the chest, revealed no abnormalities.

On August 15, a small left temporal occipital bone flap was reflected, and after the occipital lobe was elevated, an incision 2 mm. in depth was made from the lateral sulcus to the lower margin of the inferior colliculus. Damage to a plexus of small vessels on the surface caused a small but smart hemorrhage; this was controlled by silver clips. When hemostasis was complete, the bone flap was replaced and sutured.

The patient awoke from anesthesia about five hours after operation. He was too drowsy to cooperate in a detailed examination, but he did not react to pinprick on the right side of the face, the right arm or the right leg, and he did respond on the left side of the body. The following morning he became comatose and about twenty-six hours after operation suddenly died.

A postmortem examination by Dr. W. A. Stryker at 6:00 p. m. on August 16 showed besides the cerebral findings, fatty degeneration of the liver, parenchymatous degeneration of the liver and the kidneys, bilateral pulmonary hyperemia and edema, marked atherosclerosis of the coronary arteries and of the descending aorta, congenital focal fibrous thickening of the left ventricular endocardium, congenital nodule on the mitral valve, primary pulmonary tuberculous complex, focal splenic hemorrhages and lipophages in the mesenteric lymph nodes, the liver and the spleen.

Neuropathologic Findings.—The brain stem was soft and edematous and had been lacerated in removal. The vertebral arteries were thickened, and the basilar artery had two hard yellowish plaques in its wall. The internal carotid arteries were thickened, and plaques were present in their walls.

In the posterior portion of the ventral nucleus of the left thalamus was a brownish area of complete softening. Extending posteriorly from this area was a small linear area of softening involving a strip along the medial aspect of the left occipital lobe about 0.5 cm. in width and 2 or 3 cm. in length, which appeared to run into the anterior part of the calcarine fissure.

Serial sections of the thalamus and the brain stem showed that the softening of the left portion of the thalamus had almost completely destroyed the nucleus ventralis posterior of the thalamus and the anterior part of the pulvinar. The softening was complete and surrounding it was a layer of gliosis. The left cerebral peduncle and left pyramid were demyelinated. The medial lemniscus was not so well myelinated on the left side in the pons as on the right side. The basilar artery showed marked intimal thickening with necrosis and fibrosis. Most of the vessels of the brain stem and the diencephalon were thickened. Unfortunately, the laceration of the brain stem at the time of autopsy was so great that the operative lesion could not be accurately delimited.

In this case, which is an example of the thalamic syndrome with somewhat more pronounced motor manifestations than usual, the hemorrhage at the time of operation and the trauma from an attempt to control it were sufficient to cause severe edema of the brain stem, which proved fatal. It is possible to say only that in this case, as far as the results of mesencephalic tractotomy are concerned, the patient appeared to have right hemianalgesia. Before section of the tract, even the slightest pinprick on the right side produced an exaggerated reaction; after the procedure, he did not respond to such stimulation on the right side although he did on the left.

CASE 2.—*Mesencephalic tractotomy was done on a patient with carcinoma of the tongue with regional metastases producing intractable pain in the right side of the neck and the face. The results were complete relief of pain, right hemianalgesia and hemithermanesthesia. Death occurred in one month. Autopsy was performed.*

A. V., 57 year old spinster, was referred to the neurosurgical service on April 3, 1941 because of severe intractable pain on the right side of the neck as the result of carcinomatous metastases from the tongue to the regional lymph glands. Three and a half years previously she had noticed a lump on the left edge of the tongue. This was removed and diagnosed as carcinoma. Recurrence developed two years later. Radium needles were inserted at this time. One month later, 3,825 roentgens (r) was given. In December 1939, recurrence was found at the margin of the former lesion, and partial glossectomy was performed with radical removal of the glands of the left side of the neck. In May 1940, still more radical extirpation was attempted after splitting the mandible in the midline. Since the last operation she had suffered considerable soreness and tenderness over the right side of the jaw and was unable to open her jaw more than 1 or 2 cm.

On March 19, 1941, another attempt was made to excise carcinomatous nodes on the right side of the jaw. The neoplasm, however, extended beneath the base of the skull and to the wall of the carotid artery. Following this last operation, she required morphine, phenobarbital and codeine daily in varying amounts. At the time of transfer to the neurosurgical service the patient was complaining of pain in the right submaxillary region radiating to the right occiput. Occasionally sharp shooting pain was present on the right side of the face.

The patient was cooperative, but her speech was difficult to understand owing to inability to open the mouth and the previous operative procedures on the tongue. There were no obvious deformities of the head. She held the neck rigidly. There was a large pack in an open wound in the right submaxillary region. The cranial nerves were normal except for a fine horizontal nystagmus on looking to the right and the left and the difficulties resulting from the previous operations on the tongue and the jaw. Cotton contact and pinprick were well appreciated over the entire face. Both corneal reflexes were active and equal.

The motor and sensory system were normal for a woman of her age and debility. The patient was unable to walk and had not done so for several months. An attempt was made to test her sensation with Frey hairs, but owing to her difficulty in talking and the obvious pain from which she suffered it was impossible to obtain accurate results.

On April 4, with the patient under anesthesia induced with avertin with amylene hydrate, mesencephalic tractotomy was carried out on the left side. A left posterior temporal osteoplastic craniotomy was made. The dura was opened with a horseshoe-shaped incision, the toe being cut along the lateral sinus. It was reflected upward. A group of small veins passing to the lateral sinus were coagulated and cut. The lateral surface of the temporal lobe was then elevated, and the tentorium cerebelli was incised to the incisura. The mesencephalon covered by arachnoid was thus exposed and the superior cerebellar artery visualized in the angle between the cerebellum and tectum mesencephali. The area was vascular, but eventually the arachnoid was separated from the vessels and retracted from the lateral surface of the mesencephalon. A special Bovie point having a lead marker 3 mm. from the end was then tested on the cerebellum, and when the strength of the current sufficient to cut readily had been obtained, it was plunged into the mesencephalon near the rostral margin of the inferior colliculus at the lateral sulcus. When the current was applied, the patient jerked, and a second cut was necessary to complete an incision toward the inferior colliculus for a distance of approximately 6 mm. The upper edge of the incision was at the ridge on the brachium of the inferior colliculus. There was no bleeding. Approximately ten seconds after the section, the patient stopped breathing for a few seconds, and then the normal respiratory rhythm was resumed. The bone flap was replaced, and the skin was closed in the usual manner.

The patient woke from the anesthesia and responded feebly four hours after the operation. She was able to move all four extremities. The right corneal reflex was absent; the left was active. On the first day after operation the patient was more responsive, complained of no pain, was able to speak in a whisper almost as well as before the operation and had no evidence of aphasia. There was suggestive right homonymous hemianopsia. Pinprick was not appreciated on the entire right side, and the right corneal reflex was absent. The pupils were 2 mm. in diameter and did not react to direct light. External ocular movements were full. Both plantar reflexes were flexor. The wound in the neck was dressed without producing any discomfort—a procedure which before the operation was agonizingly painful to the patient. She had some difficulty in

swallowing. On the third postoperative day the patient had no particular complaints. She carried out finger-nose and heel-knee tests well on the two sides. The grip was poor but equal on the two sides. There was right hemianalgesia except for a slight appreciation of pinprick on the right leg. Position sense of the right hand was intact. She showed no evidence of aphasia.

On April 10, six days after operation, she was examined in detail. She complained of no pain except at the site of the cerebral operation. Both pupils were small but reacted well to direct and consensual light. External ocular movements were full except for limitation of the upward gaze. The right palpebral fissure was larger than the left. There was no facial weakness. The right corneal reflex was absent and the left present. The right side of the face was practically analgesic. The patient appreciated pinprick on the right side only occasionally and then considered it much duller than on the left side. Heat and cold were occasionally appreciated as such on the right side of the face. The line of division between normal and abnormal was slightly to the right of the midline. Touch was equally keen on the two sides, and tickle was the same on the two sides. Pinprick appeared to be appreciated on both sides of the tongue, but owing to the partial glossectomy, it was difficult to be certain that the anatomic right side of the tongue was being stimulated. Hearing, as tested by the spoken voice and tuning fork of 128 cycles per second, was normal bilaterally. Swallowing was difficult. The patient's voice was husky but not much different from what it was before operation. The tendon reflexes were active throughout. Both plantar reflexes were flexor. The abdominal reflexes were absent bilaterally. Pinprick was appreciated occasionally on the right leg but not at all on the abdomen, the thorax or the right arm. The division between normal and abnormal seemed to be slightly to the right of the midline over the chest and the abdomen. Cotton contact was appreciated well over the trunk and the upper extremities, although it was occasionally missed on both legs. Position sense was intact throughout. Vibratory sensation was slightly but equally decreased in both legs and normal in the arms. Stereognosis was slightly but equally impaired in both hands. The patient did not appreciate heat or cold on the right arm and only occasionally on the right leg. She was able to move all four extremities through a full range of movement. Coordination and muscle tone were normal.

On April 20, the patient began to have so much difficulty in swallowing that tube feeding was instituted. At this time, peripheral right facial weakness was noted. The patient was comfortable, although occasionally she complained of aching in the right arm, which was relieved by massage.

On April 23, her condition was much the same as previously. Right hemihypalgesia was present, but there was increased appreciation of pinprick and temperature below the mid thigh on the right leg, although these modalities were not appreciated normally in this region. The strength was good in all four extremities. The tendon reflexes were active and equal.

Metastatic nodules were felt in the left submaxillary region on April 27. The patient complained of pain in the neck and aching in the region of the right shoulder. Breathing became more difficult due to tracheal obstruction, and the patient was apprehensive. For the first time since the mesencephalic tractotomy, she was given morphine. By that means she was kept in a stuporous condition until she died of bronchopneumonia on May 1.

Neuropathologic Findings.—Permission was given for examination of the head. On removal of the calvarium, the brain appeared grossly normal with the exception of a wide incision on the lateral surface of the left mesencephalon. The

lower end of the incision was at the lateral sulcus, approximately 4 mm. from the anterior margin of the brachium pontis. It was 2 or 3 mm. in width and extended dorsally across the lower margin of the brachium of the inferior colliculus in the direction of the caudal extremity of the superior colliculus. The incision was 7 mm. in length (fig. 1). The temporal lobe appeared normal, and there were no softenings.

Serial sections were made of the rostral portion of the pons, the mesencephalon and the caudal part of the diencephalon. They were stained for cells by Nissl's technic and for myelin by the Smith-Quigley method. The lesion was seen to begin near the caudal border of the mesencephalon as a triangular zone, the lower margin of which pierced the lateral sulcus. It extended inward for a distance



Fig. 1 (case 2).—Photograph of the lateral surface of the mesencephalon after removal of the occipital lobe, the cut surface of which is seen at the left. The lesion is marked in black; *BP*, basis pedunculi; *CC*, corpus callosum; *I*, brachium colliculi inferioris; *SA*, arteria cerebelli superioris; *SC*, colliculus superior; *SL*, sulcus lateralis mesencephali; *IV*, nervus trochlearis.

of 5 mm. At this point the medial lemniscus was inferior to the lesion, but the fibers of the lateral lemniscus were sectioned with the exception of a few lying along the superolateral margin of the inferior colliculus. Traced anteriorly, the lesion was seen to maintain its lateral portion, its inferior border following the lateral sulcus. It extended into the mesencephalon for a distance of 1 cm. at the junction between the inferior and the superior colliculi (fig. 2). It had destroyed the inferior portion of the spinothalamic and spinotectal tracts, the brachium of the inferior colliculus, a part of the central tegmental pathway and

the most dorsal portion of the medial lemniscus, including the secondary trigeminal tract. It did not involve the fibers of the brachium conjunctivum or the fibers of the third nerve. The most anterior portion of the lesion extended to the junction of the medial geniculate body and the mesencephalon, destroying at this level a few fibers of the lateral and medial lemnisci.

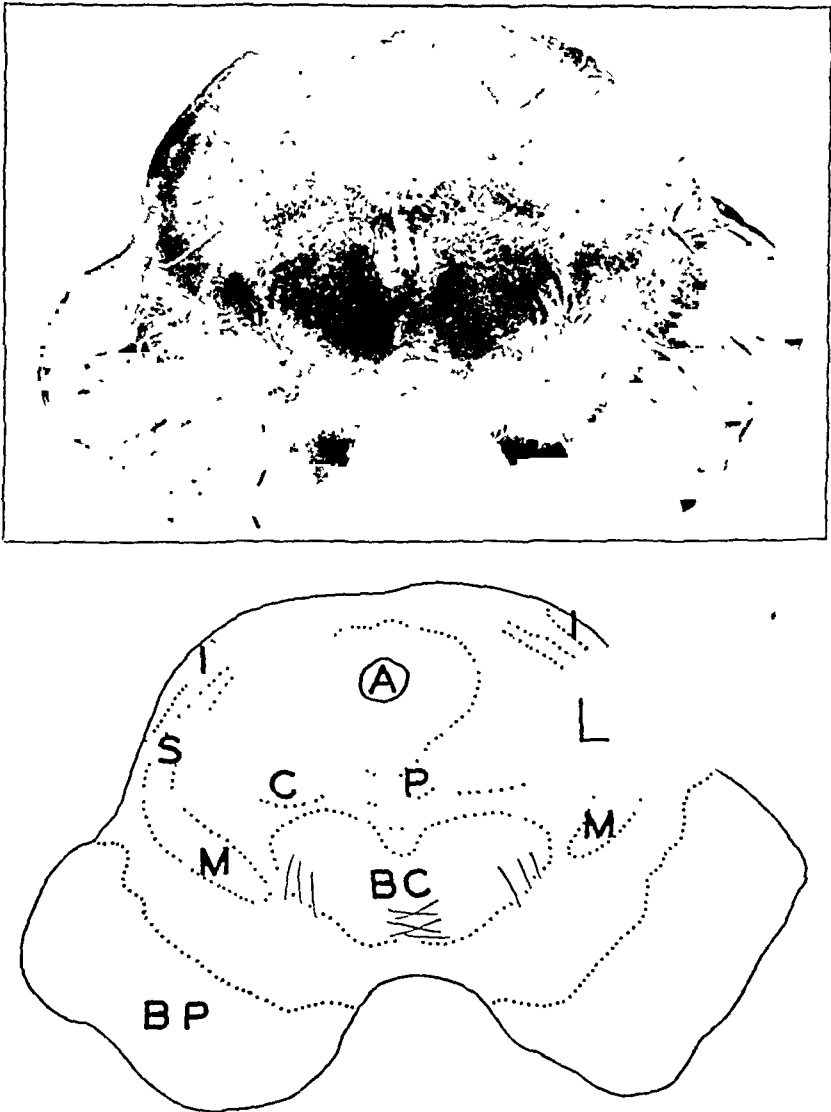


Fig. 2 (case 2).—An untouched photomicrograph of a section at the point of maximum damage to the mesencephalon (immediately caudal to the superior colliculus) and a sketch of the section with the tracts labeled: *A*, aqueductus sylvii; *BC*, brachium conjunctivum; *BP*, basis pedunculi; *C*, tractus centralis tegmenti; *I*, brachium colliculi inferioris; *L*, lesion; *M*, lemniscus medialis; *P*, fasciculus longitudinalis medialis; *S*, tractus spinothalamicus. The section was stained by Smith-Quigley technic for myelin; $\times 3$.

In this case, mesencephalic tractotomy gave complete relief from intractable pain in the neck without producing evidence of motor or pro-

prioceptive impairment of the extremities. It is impossible to say that this patient had no neurologic defect other than the loss of pain and temperature on the right side because she was unable to be on her feet. It is possible that she might have exhibited unsteadiness on walking had she been strong enough to stand. However, she did not complain of any weakness. She did notice at times an aching in the right arm, and she did state that the right arm did not feel normal, but this was only when she touched it with the left hand. The right arm could be used for normal purposeful movements.

COMMENT

These cases demonstrate the feasibility of differential section of the pain and temperature pathways at the level of the mesencephalon preserving the tactile and the proprioceptive fibers. Although technically the procedure is not extremely difficult, it is not one to be undertaken lightly owing to the danger of hemorrhage in a restricted field. The operation has a considerable mortality, although this may become less as one gains familiarity with the procedure. At times it may not be possible to attempt the section because of the vascular plexuses about the mesencephalon. In 1 case the attempt was abandoned after finding the mesencephalon almost completely covered with vessels and distorted by the local lesion. When successful, however, the procedure will completely relieve unilateral intractable pain without impairing the motor function of the extremities or producing annoying subjective paresthesia.

Topical Localization of Pain Fibers in the Mesencephalon.—The second case allows limited conclusions regarding the topical localization within the spinothalamic tract. It has previously been suggested² that the fibers of the spinothalamic tract from the lower extremities lie superiorly to those from the trunk and the upper extremity at the level of the mesencephalon. In the second case the appreciation of pain and temperature returned to a considerable degree in the lower extremity. This sparing is presumably due to the intact superior portion of the spinothalamic tract. The general somatotopical arrangement of the pain fibers at the mesencephalon would then be from dorsal to ventral—leg, abdomen, arms and face. In order to obtain complete hemianalgesia, the incision must be carried from the lateral sulcus to the superior margin of the brachium of the inferior colliculus.

Secondary Trigeminal Pathways.—Neuroanatomists have been uncertain of the secondary trigeminal pathways owing to conflicting experimental reports. As a result of the studies of Wallenberg³ and

3. Wallenberg, A.: Secundäre sensible Bahnen im Gehirnstamme des Kaninchens, ihre gegenseitige Lage und ihre Bedeutung für den Aufbau des Thalamus, Anat. Anz. 18:81-105, 1900.

van Gehuchten⁴ on rabbits, it was considered for many years that the dorsal secondary trigeminal tract conveyed fibers from the spinal nucleus of the trigeminal nerve. This bundle of fibers lies in the reticular substance just lateral to the posterior longitudinal fasciculus in the upper portion of the pons and the mesencephalon. Recent experimental evidence has cast doubt on this hypothesis.⁵ The present study makes it still less likely, because the dorsal secondary trigeminal tract was not damaged in case 2, in which the face was practically analgesic on the right side. The secondary pathway from the spinal trigeminal nucleus lies in the lateral portion of the medial lemniscus and reaches the surface near the lateral sulcus of the mesencephalon. Since these fibers were damaged by the lesion in case 2, the conclusion that they represent the secondary pathways from the spinal nucleus of the trigeminal nerve seems justified.

Corneal Reflex.—It is of interest to note that the corneal reflex was diminished in the first patient before operation as the result of the thalamic lesion. (Serial sections of the brain stem showed no lesion of the fifth or seventh cranial nerves or their nuclei.) In the second case, the corneal reflex was practically absent after mesencephalic tractotomy, and in this case serial sections of the brain stem failed to show a lesion of the nuclei of the fifth or seventh cranial nerves. It is therefore evident that there must be a suprasegmental arc for the corneal reflex. This cerebral arc of the corneal reflex has been demonstrated and discussed previously.⁶ The present cases present evidence suggesting that the afferent limb of this reflex arc consists of fibers of the secondary trigeminal tract passing with the spinothalamic fibers.

SUMMARY

A method is described for the differential section of the sensory pathways in the mesencephalon. The pain and the temperature fibers are cut, leaving intact the tactile and the proprioceptive fibers. Such a section will give relief from unilateral intractable pain without producing paralysis or numbness.⁷ Two cases in which the operation was used are described.

950 East Fifty-Ninth Street.

4. van Gehuchten, A.: Recherches sur les voies sensitives centrales, La voie centrale du trijumeau, *Névraxe* 3:235-261, 1901.

5. Walker, A. E.: The Origin, Course and Terminations of the Secondary Pathways of the Trigeminal Nerve in Primates, *J. Comp. Neurol.* 71:59-89, 1939.

6. Walker, A. E.: The Cerebral Arc of the Corneal Reflex, *J. Nerv. & Ment. Dis.* 92:569-578, 1940.

7. Since this paper was submitted for publication, mesencephalic tractotomy has been performed for intractable pain in 3 additional cases without an operative death. Two patients stated that the contralateral half of the body felt dead, and 1 of these had a disagreeable but not painful sensation in the affected arm at times. All 3 were relieved of pain.

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CYST OF THE COMMON DUCT

BEVERLY CHEW SMITH, M.D.

NEW YORK

A cyst or idiopathic cystic dilatation of the common duct is comparatively rare. The number of cases in an individual physician's experience is too small to formulate a definitive plan of treatment. The literature of the past is lacking in follow-up reports. Recent chemical methods for combating bleeding in cases of jaundice have possibly changed the surgical emergency of this condition. Most reported cases lack laboratory observations of the chemistry associated with jaundice.

I have been able to collect 181 cases from the literature. Two additional cases are here reported from the Presbyterian Hospital. They are the only cases of the kind on file among the records of 757,000 cases.

Many factors have been advanced as the cause of this condition. The most logical encountered is that given by Yotuyanagi, namely—the inequality of proliferation of the epithelial cells when the common duct is a solid cord of cells and while it is becoming a patent tube. This occurs about the eighth week of fetal life.

It is of interest that most of these cases have occurred in female patients before 25 years of age. A number have been pregnant when the cyst became clinically obvious.

The cyst wall has frequently been fibrous tissue without lining epithelium.

The only case found with a long follow-up was that of Judd and Greene in which the cyst was anastomosed to the duodenum on Feb. 4, 1927. This patient replied to a questionnaire from the Mayo Clinic in February 1932 that she was perfectly well. However, on Jan. 4, 1940, her local physician sought by letter to learn what operative procedure had been performed on her because "at the present time she is having symptoms similar to gallbladder disease." This thirteen year follow-up report thus leaves one in doubt as to the true condition existing in this patient at present.

Read at a combined meeting of the New York Surgical Society and the Philadelphia Academy of Surgery, New York, Feb. 12, 1941.

From the Surgical Service, Presbyterian Hospital, and the Department of Surgery, Columbia University College of Physicians and Surgeons.

REPORT OF CASES

CASE 1.—M. D., a 20 year old unmarried woman, was admitted to the Presbyterian Hospital on Sept. 23, 1940, complaining of a mass in the right upper part of the abdomen which had steadily enlarged in the past five weeks, jaundice of three weeks' duration, itching, loss of appetite, loss of weight and discomfort in the region of the abdominal mass. She had always lived on Long Island. Her babyhood was normal. In childhood she was exposed to her mother, who died of pulmonary tuberculosis in 1927, and one sister, who had the disease but recovered.



Fig. 1.—Photograph showing outline and size of cyst.

Her past health had been excellent except for an attack of painless jaundice lasting one month in 1932 at the age of 12. She was deeply jaundiced at that time; her skin itched, but she could not recall having had clay-colored stools. Other than this she had always been healthy and active and had engaged in strenuous outdoor exercise.

About Aug. 16, 1940, she noticed a hard nontender mass in the right upper part of the abdomen, measuring about 2 by 2 inches (5 by 5 cm.), just below the costal margin. In a week, it doubled in size. In two more weeks, it filled the right half of the abdomen. During the second week that she noticed the mass she became jaundiced. Her skin itched, and her jaundice steadily deepened. Three weeks after she noticed the mass and one week after the onset of jaundice,

she noted clay-colored stools. She was never really acutely ill and was nauseated and vomited only after taking certain fatty foods.

When she first noted the mass, she felt a dull aching abdominal pain in the region of the mass, but this subsided and did not recur. She was constipated and lost 30 pounds (13.6 Kg.), and her appetite failed. There were no tarry stools. Her menstrual periods were normal.

On admission, the temperature was 100 F.; the pulse rate, 100; the respiration rate, 20. The blood pressure was 124 systolic and 100 diastolic. She was thin, deeply jaundiced and chronically ill. There were many scratch marks over the

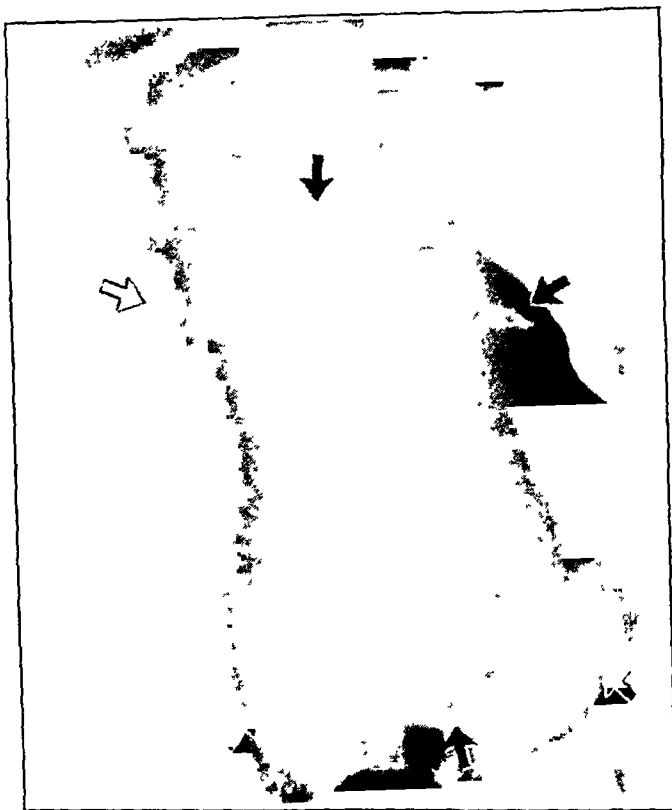


Fig. 2.—The cyst (outlined by arrows) has pushed the stomach to the left and the duodenum posteriorly so that it has been hidden by the stomach.

whole of her body, and on the left wrist there was an area of ecchymosis 3 by 9 cm., which occurred without a history of trauma.

A nontender firm slightly irregular mass 25.5 by 30.5 cm. which gave the sensation of containing fluid extended from the right costal margin to the right anterior superior iliac spine, beyond the umbilicus and could be balloted in the right flank. Its lower edge moved with respiration. The liver was discernible to percussion to the fifth interspace in the midclavicular line and to the ninth rib in the midaxillary line. Rectal examination was negative except that the feces were black. There were no hemorrhoids. The pelvic adnexa on rectal examination were normal. A diagnosis of cyst of the right upper part of the abdomen was made; the cyst was considered to be pancreatic, hepatic, choledochal or mesenteric.

The significant laboratory findings before and after operation may be summarized conveniently as follows:

Initial blood study: red cell count, 3,000,000; hemoglobin content, 55 per cent; white cell count, 11,900, with 55 per cent polymorphonuclears and 34 per cent small lymphocytes; Kline test, negative; serum cholesterol, 248 mg. per hundred cubic centimeters.

9/25/40 Bleeding time, 30 seconds; clotting time, 3 minutes.

9/26/40 Transfusion of 500 cc.

9/29/40 Transfusion of 500 cc. (citrated blood).

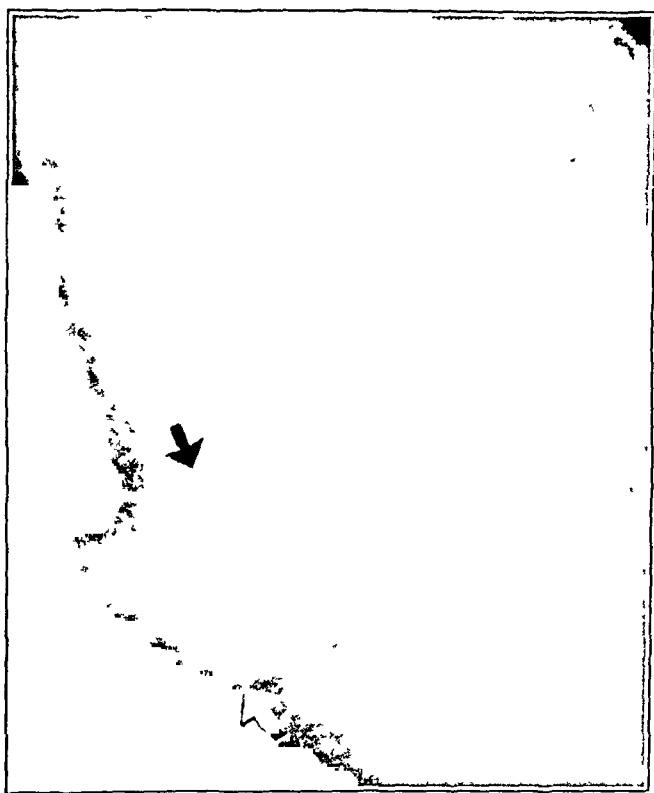


Fig. 3.—Arrows indicate the degree of dilatation of the duodenum.

11/30/40 Two transfusions of 500 cc. each.

9/27/40 Cystic fluid: protein, 0.34 per cent; bile acid +; amylase and lipase 0; bilirubin 0.

9/28/40 Amylase and lipase present in bile drainage.

11/ 7/40 Protease 0; carbon dioxide, 55 volumes per hundred cubic centimeter's

9/24/40 Cephalin flocculation test, negative.

1/ 6/41 Cephalin flocculation test, negative.

11/ 7/40 Benzoic acid liver test: 3.2 Gm. excreted in urine.

1/21/41 Bromsulfalein liver test: 50 per cent retained at end of five minutes, trace in blood at end of thirty minutes

- 11/19/40 Blood calcium, 10.4 mg. per hundred cubic centimeters; nonprotein nitrogen in blood, 22 mg. per hundred cubic centimeters.
- 11/25/40 Prothrombin time normal.
- 1/24/41 Urobilin output in stool, 8,500 units per day.
- 1/ 6/41 Red blood cell count, 3,600,000; hemoglobin content, 80 per cent; white blood cell count, 4,300, with 21 per cent polymorphonuclears and 61 per cent small lymphocytes; agglutination test with sheep red blood cells in 1:8 serum dilution (Forssman antigen), negative for mononucleosis.



Fig. 4.—The cyst (outlined by arrows) has displaced the colon, as outlined by the enema of barium sulfate, into the pelvis.

- 9/29/40 Bile drainage, 310 cc.
- 10/ 1/40 Bile drainage, 800 cc.
- 10/ 5/40 Bile drainage, 500 cc.
- 9/24/40 Urine: bile 4+.
- 10/27/40 Urine: bile 0.
- 9/24/40 Stool: bile 0; guaiac 4+.

The roentgen studies before and after operation may be summarized as follows:

- 9/25/40 *Gastrointestinal series:* The abdominal mass displaced the stomach and the duodenum forward and to the left and the transverse colon downward. The mass could not be separated from the liver.

- 9/26/40 *Right intravenous pyelogram:* The mass filled the right portion of the abdomen. The outline of the right kidney was indistinct but normal. The left kidney was not clearly seen. The small intestines were pushed to the left. The right ureter, the renal pelvis and calices were well filled with dye. The ureter was normal. There was slight dilatation of the right renal pelvis and calices.
- 10/10/40 Two weeks after marsupialization of cyst: The cyst sac was filled with hippuran; it was triangular and measured 15 by 7 cm. A narrow tract on its superior and lateral border seemed to be in direct relation with the hepatic ducts. No opaque fluid entered the duodenum. The cyst held 80 cc.

TABLE 1.—*Summary of Data from Studies of Blood of Patient M. D.*

Date	Serum Bilirubin Mg. per 100 Cc.	Phosphatase, Mg. per 100 Cc.	Phosphatase (Bodansky Units per 100 Cc.)	Hematocrit Value	Plasma	
					Specific Gravity	Protein, Per Cent
9/24/40	20	3.7	19.5	20.8	1.0239	5.78
9/26/40	31	3.7	22.1
9/27/40	30	3.8	21.8
(First operation *)						
9/28/40	20	37.1	1.0223	5.4
9/29/40	15	36.2	1.0220	5.14
10/ 7/40	40.9	1.0280	7.18
10/15/40†	6.1			
10/18/40	5.2f...	7.3
10/25/40	3			
10/31/40	2.7			
11/13/40	1.3			
11/30/40			
(Second operation ‡)						
12/ 9/40	Negative	3	3.3			
12/30/40	3.4	9.4			
1/ 6/41	Negative	3.3	6.6			

* Marsupialization of the cyst.

† Administration of desiccated hog bile in capsules (Parke-Davis desicol) started; one capsule three times a day increased to thirty-three capsules per day. Each capsule contains 5 grains (0.325 Gm.) of desiccated bile, equivalent to 2.5 cc. of whole fresh bile.

‡ Anastomosis of the cyst to the duodenum.

- 10/18/40 Intravenous injection of soluble iodophthalein failed to reveal a gall-bladder shadow.
- 10/20/40 Hippuran in the cyst showed a slight diminution in the size of the cyst since similar procedure ten days before and no communication with the duodenum. The cyst held 30 cc.
- 1/ 2/41 Thirty-two days after the cyst was anastomosed to the duodenum. Gastrointestinal series: The duodenum showed slight constriction at the cyst anastomosis site. The cyst filled and emptied readily through the anastomosis. Barium sulfate proceeded from the duodenum into the small intestine normally. There was a slight barium residue in the cyst at twenty-four hours.

1/11/41 Roentgenogram of the chest essentially negative.

1/29/41 Gastrointestinal series: Barium sulfate failed to enter the cyst.

The patient was given bile salts, vitamin K and a transfusion and because of rising serum bilirubin was subjected to operation on September 27.

First Operation.—The abdomen was opened with infiltration local anesthesia through a 2 inch (5 cm.) retracted upper right rectus incision. The patient was too ill and deeply jaundiced to permit of other than a palliative and exploratory procedure. A cystic mass was encountered which was too large to be delimited.



Fig. 5.—The cyst was injected with hippuran twelve days after marsupialization. It held 80 cc. The hepatic radicles partially fill at the upper right margin of the cyst.

It was aspirated. The first white mucoid fluid was followed by dark brown fluid without odor. A sucker aspirated 5,200 cc. of similar fluid.

The duodenum lay anterior on and to the left of the cyst wall; the small intestines were pushed to the left into the pelvis; the transverse colon was below it and also in the pelvis; the stomach was upward and to the left. The gall-bladder was in its normal position; it was edematous and about twice normal size. The liver was not apparently cirrhotic; its lobes were normal. About 100 cc. of bile-stained clear nonodorous fluid was recovered from the peritoneal cavity.

The cyst was opened, explored and found to have a smooth wall without calcification or calculi. It extended to the hilus of the liver. No communication could be made out with the hepatic ducts, the gallbladder or the duodenum, and no bile drained into the cyst while it was being observed. The pancreas could be felt through the posterior wall of the cyst. The foramen of Winslow was patent. The common duct as such could not be identified in the gastrohepatic omentum. Because the nature of the cyst could not be determined, a piece of the wall was taken for pathologic examination. The cyst was marsupialized by suture to the anterior rectus sheath, and a rubber tube was sutured into it. The patient stood

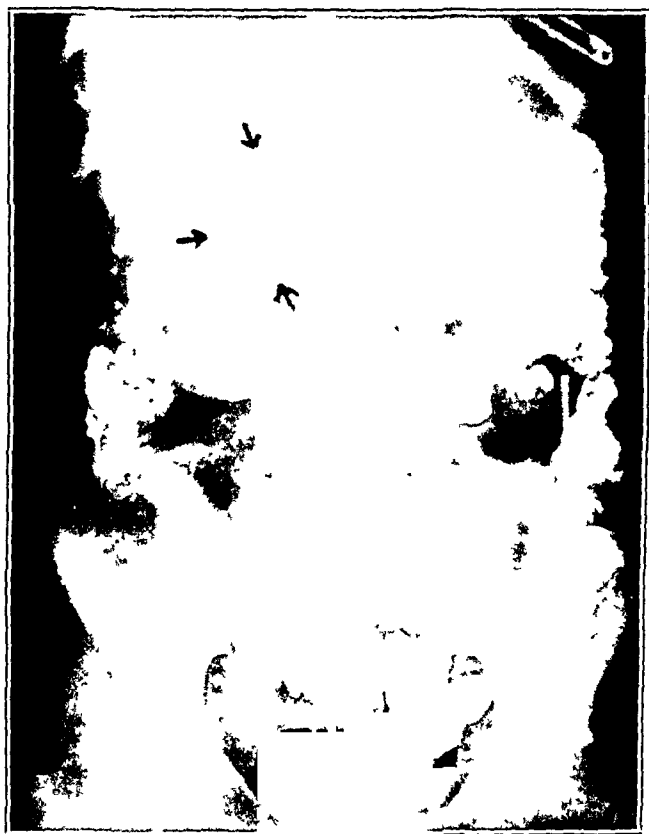


Fig. 6.—Arrows indicate the retention of barium sulfate in the cyst twenty-four hours after barium sulfate was given by mouth for gastrointestinal study. This study was made thirty-three days after the cyst had been anastomosed to the duodenum.

the procedure well. She was given a second transfusion on her return to the ward with 500 cc. of citrated blood.

Pathologic Examination.—The cyst wall consisted of a piece of greenish yellow tissue, one surface of which was smooth and glistening; the other surface showed hemorrhagic foci. It was fixed in Bouin's fluid. Microscopic examination revealed the cyst wall to be composed of dense fibrous tissue. It was avascular and showed

a mild polymorphonuclear infiltration. The inner surface was covered by a layer of acidophilic coagulum. There was no evidence of epithelium.

Nine hours after this operation, clear golden yellow bile began to drain from the cyst and continued to do this until a second anastomosing operation was done on November 3. For thirty-seven days between the operations, the patient's stools

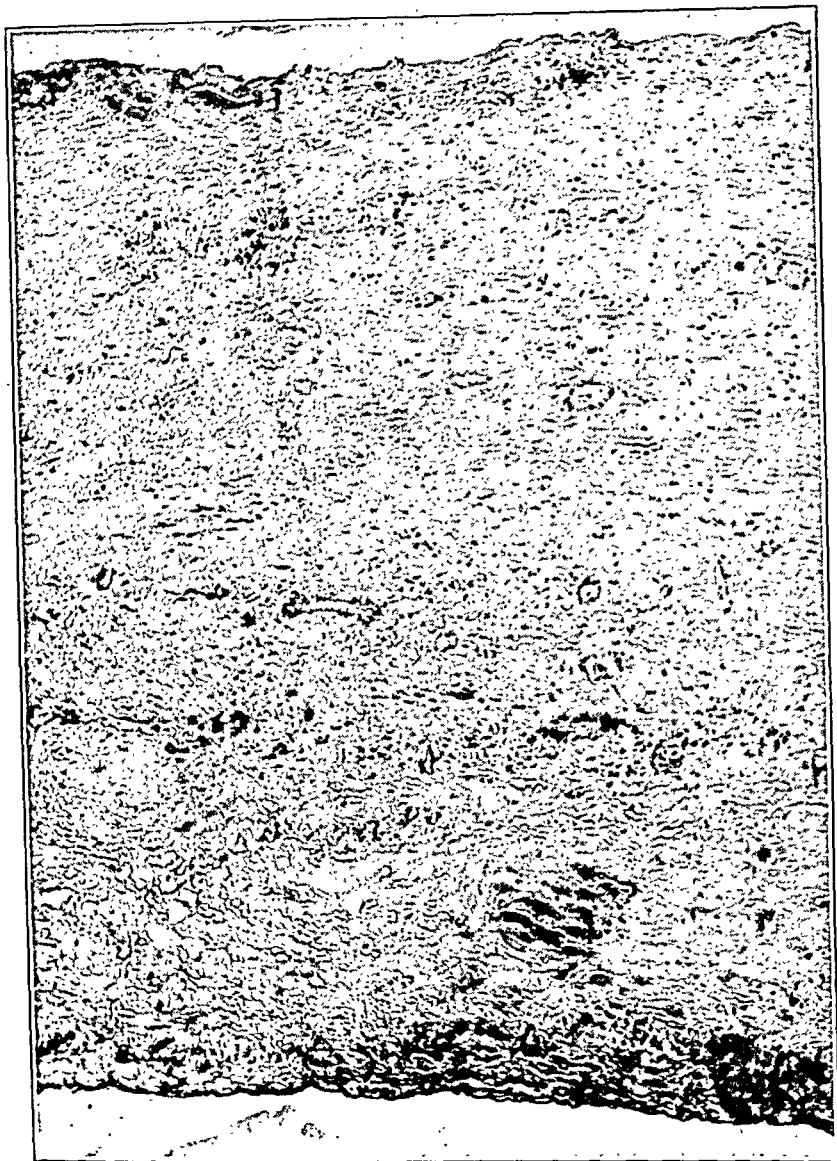


Fig. 7.—Photomicrograph of the cyst wall. For description see text.

were continuously free of bile. The bile output varied from 300 to 800 cc. in twenty-four hours, averaging 500 cc. There was little excoriation of the skin about the cyst opening.

Postoperative Course.—The jaundice gradually diminished until the serum bilirubin on the fifty-third postoperative day was 1.3 mg. per hundred cubic centimeters. The urine phosphatase and cholesterol became normal. The cyst continued

to drain the entire biliary output. No communication could be established by roentgen examination with the duodenum, but a suggestion of the hepatic ducts was noted on one occasion. The stool was negative for bile.

The patient was given vitamin K and bile salts, and a study of fat digestion with and without bile salts was made (table 2). She gained 8 pounds (3.6 Kg.) and became ambulatory.

Second Operation.—Because of continued bile drainage an anastomotic procedure was deemed necessary, and on November 30, with the patient under anesthesia induced with nitrous oxide and oxygen through a transverse upper right rectus incision the abdomen was opened by Dr. Allen O. Whipple, Dr. Beverly C. Smith assisting, and the following observations were made:

The cyst was a large collapsed sac measuring roughly 12 by 18 cm. and extending from the portal fissure to the opening of the cyst in the anterior

TABLE 2.—*Fat Absorption in a Case of Complete Bile Fistula Following Marsupialization of a Cyst of the Common Bile Duct**

Date	Weight of Patient, Lb.	Fat Consumed,† Gm.	Fat in Stool, Gm.	Fat Absorbed, Per Cent	Bile Capsules, per Day ‡
10/24/40	85 (38.6 Kg.)	50	48	4	18
10/29/40	87 (39.5 Kg.)	100	75	25	18
11/12/40	90 (40.8 Kg.)	100	84	16	33
11/18/40	91½ (41.5 Kg.)	100	67.5	33	33
11/30/40	Operation: anastomosis of the cyst with the duodenum				
12/20/40	33.7	4.87	86	
1/22/41	66	6.7	..	
1/23/41	66	6.7	90	
1/24/41	66	6.7		

* The following note on these fat absorption studies was made by Dr. Louis Bauman: "While I have made no exhaustive search of the literature, my impression is that this patient afforded a rare opportunity to study fat absorption in the complete absence of bile and uncomplicated by other factors, such as partial or complete pancreatic obstruction. The striking difference observed after reentrance of bile into the intestine is ample confirmation of its controlling influence on fat absorption in the human being."

† Weighed diet.

‡ Desleol (Parke, Davis & Co.).

abdominal wall. It was intimately connected with the duodenum and was impossible to separate from this structure without grave risk of creating a fistula in the posterior aspect of the duodenum. It was not certain that the cyst was not adherent to the portal vein. In the upper right portion of the cyst, the opening of the common hepatic duct was seen, and the index finger could be introduced, feeling the opening of the two hepatic ducts into which a probe easily passed into both lobes of the liver. Definite communication between the cyst and the gallbladder could not be established. Aspiration of the gallbladder brought away no bile. No communication could be established between the cyst and the duodenum. The duodenum was opened, and the papilla of Vater was probed with a fine probe which extended into the pancreatic duct well down into the pancreas, but no communication could be established with the cyst from this direction.

It was felt that the procedure of choice was anastomosis of the opening of the cyst with the duodenum. It was felt that attempted excision would endanger the duodenum and the portion of the common duct which the cyst constituted. The cyst was therefore anastomosed to the duodenum with chromic catgut, allowing

an opening of approximately 2 or 3 inches (5 or 7.6 cm.) in each viscus. The fusion between the cyst and the duodenum made a posterior seroserosus suture unnecessary. On the anterior wall, a seroserosus suture of C silk was placed, and the abdominal wall was closed in layers with catgut and silver wire, because the preoperative wound was infected and possible evisceration was anticipated. The patient received a transfusion of 1,000 cc. of whole citrated blood during the procedure.

Postoperative Course.—The postoperative course was marked by a febrile reaction of 103 F., which became normal by the fourth day. The chest remained clear. Beginning the first week after operation, the patient had a daily rise in temperature to 101 or 102 F. without local signs of infection other than in the wound. The blood cultures and urinalysis were negative. A roentgenogram of the chest showed normal lungs. There was no clinical evidence of cholangitis. She felt perfectly well and did not complain of pain. The gastrointestinal tract functioned normally. The serum bilirubin became negative; the stools were brown and contained bile; the urine became free of bile; serum phosphatase reached 3.5 Bodansky units on the thirty-first day. The cephalin flocculation test remained negative.

On the thirty-ninth postoperative day, the blood count revealed: 3,600,000 red blood cells with 80 per cent hemoglobin, and 4,300 white blood cells with 33 per cent neutrophils, 1 per cent eosinophils, 8 per cent monocytes and 58 per cent lymphocytes. An agglutination reaction with Forssman's reagent was negative for mononucleosis.

Wound healing was complicated by numerous superficial sinuses around the silk sutures which were successively emitted from the wound. A wound culture revealed a nonhemolytic *Staphylococcus aureus*. It was thought that this was largely responsible for the patient's elevation of temperature. By the forty-sixth day, the temperature had returned to normal.

The bacteriologic findings may be summarized as follows:

- 9/30/40 Culture from scratch marks in skin: hemolytic *Staphylococcus aureus* and *Streptococcus viridans*.
Free peritoneal fluid: no growth.
Cyst fluid: no growth.
- 10/15/40 Bile draining from cyst: *Salmonella* group (gram-negative rods).
- 10/16/40 Bile draining from cyst: 330,000 organisms per cubic centimeter; after standing twenty-five hours in icebox, 1,600,000 organisms per cubic centimeter.
- 11/20/40 Bile from cyst: hemolytic *Bacillus coli*; no anaerobes.
- 11/22/40 Sulfathiazole given, 7 Gm. for one day; severe nausea; drug stopped.
- 12/ 4/40 Wound culture at second operation: nonhemolytic *B. coli*, *Staph. aureus*, no anaerobes.
- 12/ 6/40 Wound culture: nonhemolytic *Staph. aureus*.
- 1/ 7/41 Blood culture: no growth.
- 1/ 9/41 Urine culture: *B. coli* in clean noncatheterized specimen.

On the thirty-fourth day after the second operation a gastrointestinal series of roentgenograms showed barium sulfate entering and leaving the cyst through the anastomosis with a small twenty-four hour residue in the cyst; the meal proceeded normally down the small intestine during the examination. On the fifty-third day, a bromsulfalein test showed 52 per cent retention in five minutes and only a trace in thirty minutes, indicating normal liver function.

The patient became ambulatory on the forty-second day after operation and gained an average of 1 pound (0.5 Kg.) a week for four weeks previous to discharge, at which time she weighed 92 pounds (41.7 Kg.). Her normal weight before the onset of this illness was 114 pounds (51.7 Kg.). Studies of fat absorption during the four weeks after operation showed that 90 per cent of the fat ingested was absorbed compared to only 4 per cent of a measured amount absorbed when all of the bile was coming through the fistula.

The postoperative course was uneventful and comfortable. She was discharged to a convalescent home on the sixty-second day with a small granulating superficial wound. At the time of writing, her wound is solidly healed except for a superficial sinus at each end which probably harbors a silk suture. The red blood cell count is 4,240,000 with 82 per cent hemoglobin, and the white blood cell count is 9,200 with 36 per cent polymorphonuclears, 41 per cent small lymphocytes, 17 per cent large lymphocytes and 6 per cent monocytes.

At the time of a follow-up examination, Oct. 15, 1941, the patient was symptomless; she weighed 121 pounds (54.9 Kg.) and had returned to her former secretarial position.

CASE 2.—M. M., a woman 28 years old, was admitted to the Presbyterian Hospital on Jan. 30, 1916, with the following history:

Since the age of 18, when she was at boarding school, she had irregular attacks of dull aching abdominal pain, jaundice, clay-colored stools and malaise. At times she would be free of symptoms for months. In 1910 (six years before admission), she had a severe attack of jaundice which lasted three weeks. Several less severe similar attacks occurred between her first pregnancy, which resulted in a spontaneous abortion at two months, and her second pregnancy, which was marked by attacks of severe pain and jaundice. She described the pain of her attacks as occurring "in the middle" of her and not radiating. Local physicians regarded her condition as gallstone colic, but operation was twice postponed because of her pregnancies. In August and October of 1915, she had particularly severe attacks of pain and deep jaundice. Surgeons thought they felt her gallbladder during these attacks.

Her past history was negative except for scarlet fever and diphtheria when she was 3 years old. In 1915, she had a tonsillectomy done at the Mayo Clinic, after which she had severe postoperative hemorrhage, which was controlled by the usual methods. Her early girlhood was healthy, vigorous and free of illnesses. Her mother and father, a brother and a sister were living and well. The patient had one living normal child.

First Operation.—Operation was performed on Jan. 31, 1916, by Drs. George Brewer and Adrian Lambert with the patient under anesthesia induced with nitrous oxide and ether.

The gallbladder was soft and flaccid. No stones were felt in any of the biliary ducts. There was a tense cystic mass the size of a grapefruit (about 12 to 15 cm. in diameter) in the head of the pancreas. This cyst was aspirated with a trocar after it was exposed by opening the lesser sac through the gastrohepatic omentum. The cyst wall was friable and about 1/16 inch (0.16 cm.) thick. The aspirated fluid resembled old blood and was thought not to have been bile. The cyst lay to the left of the ducts, was adherent to and communicated with the common and cystic ducts at about their juncture. The cystic duct was elongated, tortuous and enlarged. The stomach and the duodenum were normal.

Procedure.—The peritoneal cavity was entered through an upper right rectus incision. The gastrohepatic omentum was incised; the cyst was exposed, aspirated

and excised from the surrounding pancreas in which it was embedded, down to its connection with the ducts, where the posterior wall was left intact for an area 2 cm. in diameter. This portion of the wall was sutured over a rubber tube which passed into the left hepatic duct. Another rubber catheter was passed downward in the sac toward the common duct and left in situ. From within the cyst no communication with the duct system could be demonstrated by a probe. (No mention is made of communication with the duodenum.) The abdomen was closed in layers. Packing was necessary to control hemorrhage from the site of the excised cyst. The patient was severely shocked by the procedure but reacted to transfusion and other treatments. A week later she was given nitrous oxide to induce anesthesia, and the packing was removed. A biliary fistula persisted. There was no bile in the stool.

Second Operation.—On March 6, 1916, a second operation was performed.

Many firm adhesions were encountered throughout the right upper quadrant of the abdomen. At the base of the sinus tract in the abdominal wall a divided hepatic duct was encountered. There was a collection of several ounces of bile-stained purulent material beneath the liver. The gallbladder was distended with bile. The stomach was adherent under the liver. The adherent duodenum was mobilized.

Procedure.—The previous scar in the right upper quadrant of the abdomen was incised and the abdominal cavity entered. The sinus tract was followed down to the divided ends of the (common) hepatic duct left at the preceding operation. A hole was inadvertently made in the gallbladder just above the ampulla. The divided duct admitted a probe into the right and left hepatic ducts. A small rubber tube was sutured into the lateral portion of the patent common hepatic duct and passed into the rent in the ampullary region of the gallbladder and out the fundus of the gallbladder through the anterior wall of the abdomen. Both openings in the gallbladder were closed with chromic catgut purse string sutures about this tube. A second tube was placed in the fundus of the gallbladder and held there by a purse string of chromic gut. The other end of this tube was placed into the duodenum through a small incision and anchored there by a similar suture with several retaining adjacent serosal sutures of plain gut between these structures. This was done because a probe passed into the hole in the ampullary region in the gallbladder could not be passed into the cystic duct. The upper portion of the cystic duct was never demonstrated. Morrison's pouch was drained, and the abdomen was closed in layers. The patient, who was severely shocked, rallied after a transfusion of 650 cc. of citrated blood.

Pathologic Examination.—The specimen consisted of a portion of a cyst measuring 8 cm. in its greatest diameter. The wall measured 1 or 2 mm. in thickness. On microscopic examination, the cyst wall was found to be composed of loose edematous connective tissue with scattered strands of smooth muscle fibers running through it. The lining consisted of a thin layer of granulation tissue infiltrated with polymorphonuclear leukocytes and round cells with necrotic tissue adherent to it. The wall was vascular with thick-walled vessels. The origin of the cyst was obscure. At one point at a small opening into the cyst, a mucous membrane of cuboidal epithelial cells with underlying short dilated mucous glands in a cellular stroma containing blood vessels was observed and was thought to be from a bile duct. Dr. A. P. Stout made the diagnosis of cyst of the common duct.

Postoperative Course.—The stools remained clay colored. Culture of bile from the sinus tract revealed hemolytic streptococcus. The fluid from the cyst gave a

positive reaction for blood, was negative for bile and showed an increased diastase reaction and a decreased degree of protein digestion by trypsin. A biliary fistula persisted up to and after her discharge on May 15. She slowly regained her strength. The cholecystenterostomy tube passed by rectum two weeks after operation. The stools at that time were dark but subsequently became clay colored and negative for bile. She had severe urticaria during the last week in the hospital.

Third Operation.—There is no record of her course from May 15, 1916 to Oct. 3, 1917, when she was operated on by Dr. W. J. Mayo at Rochester, Minn. Dr. Waltman Walters furnished me with the data hereinafter reported from her record at the Mayo Clinic.

Procedure.—Hepaticocholecystoduodenostomy and partial cholecystectomy were performed through a right rectus incision. On opening the abdomen, dense adhesions of the stomach, the duodenum, the liver and the transverse colon were encountered. It was difficult to get through the adhesions and down to the seat of the trouble. Finally, a way was found into the remnant of the gallbladder, which was extremely thick walled and almost filled with small stones and inspissated foul bile. After evacuating its contents, the surgeon's finger was passed down into the end of the hepatic duct. Apparently the entire main hepatic duct was absent, for the finger passed at once to the right and left main branches. By passing the finger into the right duct about $\frac{1}{4}$ inch (0.64 cm.), the secondary division of the right duct was reached. Any one of the ducts would admit the finger, and the line of union between the gallbladder and the hepatic duct was the size of a thumb. An enormous quantity of foul bile and a large number of stones of the variety formed in the hepatic ducts were evacuated from the liver ducts. Whether the flow of bile, which previously took place intermittently into the duodenum, passed through some direct connection with the common duct or indirectly through the cystic duct, could not be readily seen; however, no great effort was made to find out, for wherever it was, it was wholly insufficient. After the hepatic ducts were cleaned out as well as possible, the gallbladder was amputated about its middle, and the mucous membrane was dissected out down to a point about $\frac{1}{2}$ inch (1.27 cm.) above the main hepatic duct. The mucous tube, which was about the size of the forefinger, was next loosened and united by a mucomucous suture to an opening made in the duodenum about $2\frac{1}{2}$ inches (6.35 cm.) below the pylorus. A 3 inch (7.6 cm.) section of no. 12 English catheter with lateral eyes was then introduced for a distance of 2 inches (5 cm.) up into the main right hepatic duct; it was passed 1 inch (2.5 cm.) into the duodenum and sutured to the duodenum. It was anticipated that this tube would pass out in due time. It was inserted to insure direct passage until union was complete. The new opening was to be permanent, as the mucous membrane of the gallbladder stump and the duodenum were to be brought in actual contact with the gallbladder tube in its entire circumference. An edge of omentum was placed over the anastomosis. Two rubber tissue drains were used—one above and one below; a short rubber tissue drain was inserted through the fistula.

Postoperative Course.—After operation, the patient's pulse rate went up to 140 the first day of the operation, decreasing rapidly and progressively to the fourth postoperative day when it was normal. At that time the temperature was 99.2 F. It continued at about this level, and the pulse rate remained normal until the early morning of the ninth postoperative day, October 11, when a rapid and progressive rise in the pulse rate and the temperature occurred. On October 12, the temperature was 104 F. by axilla, and the pulse rate was 150. A note on the hospital record

shows that biliary fistula developed on the day of operation. On the eighth day, bleeding occurred from the sinus in the incision, and a transfusion was administered. She died on the tenth postoperative day.

Autopsy.—Autopsy was performed by Dr. W. W. Bissell. The body was that of a well developed markedly emaciated young woman about 30 years of age. There was a recently made, surgically repaired, curving laparotomy wound extending from the ensiform cartilage and extending 5 cm. to the right of the midline. This wound was 16 cm. long and ended at a point 5 cm. to the right and 5 cm. below the umbilicus. About the center there was a gaping area, measuring 3 by 2 cm., and a smaller one just to the right, about 1 cm. in diameter. This area contained dark clotted blood. At a point 2 cm. above this was another opening, also measuring 1 cm. in diameter, and about 8 mm. deep. This presented a reddish base. There was no discharge.

On opening the laparotomy wound, only a slight amount of healing was found. The great omentum was slightly adherent to the anterior parietal peritoneum adjacent to the laparotomy wound, but when discrete fibrinous adhesions all about the lower border of the right lobe of the liver were separated, numerous clots of blood were encountered. All told, there was approximately 500 cc. of blood clot, and after removing these nearly a liter of fluid blood was removed.

Before attempting to ascertain with exactness the lesions about the site of the gallbladder and the bile ducts, the liver, the stomach and the diaphragm were lifted out of the body, together with all the attached abdominal viscera, and were reflected downward in the regular way so that examination proceeded from behind. In this manner, when the hepatic duct was about to be opened, it was learned that it was united to the duodenum. A stump of an opened gallbladder was found at its usual site, but even after a most prolonged search, no cystic duct was discoverable. The common hepatic bile duct was greatly widened. All told, it measured 2 inches (5 cm.) in circumference. Careful search was made for the common bile duct. To begin with, the portal vein was opened and traced out through its main tributaries. It presented no abnormality, and it occupied its usual position and took its usual course. The common bile duct, when examined from behind, usually takes its position just to the right of the course of the portal vein, and search was made for this common bile duct in this position. Dense fibrous tissue was encountered, but no duct could be found.

The pancreas was cut transversely approximately at the junction of the middle third and the tail. By this means, the gaping mouth of the pancreatic duct was found, and the duct of Wirsung was traced throughout its course. Instead of taking the normal course parallel to the long axis of the pancreas and then turning abruptly downward and medianward into the ampulla of Vater to enter the duodenum, this duct turned upward and medianward, and its opening into the duodenum was found without difficulty. Careful search was then made for the opening of the common bile duct in this position, but none was found. The ductus pancreaticus Santorini was then traced, and it was found to bear no relation to a bile duct. It is thus evident that after this careful search no common or cystic bile duct was found. In the case of the cystic duct it is certain that it was either absent or completely obliterated in the fibrous tissue about the gallbladder notch. With regard to the common bile duct the same is true. Yet some remnants of the duct presumably must have functionated. The mucous lining of the duodenum was so softened that no trace of a common duct in the duodenum could be found. The pancreas was enlarged to approximately twice the normal size. In the areolar tissue all about it there was considerable

watery, slightly jelly-like material of inflammatory edema—inflammatory because practically all of the pancreas was replaced by greenish fibrinopurulent necrotic material. Dr. Bissell stated that he had never observed more extensive pancreatitis. All about the pancreas in the areolar tissues, there were numerous small chalky white areas of fat necrosis. This fat necrosis, however, was confined to the immediate vicinity of the pancreas itself.

The liver was of approximately normal size. It was adherent all along its lower border to the diaphragmatic peritoneum, but above it was practically free. On the capsular surface numerous small areas of brownish green discoloration could be seen, and on surfaces made by sectioning, these areas of discoloration were found to be areas of coagulation necrosis. They were discrete and distinct, and they were all greenish black. There was no bile retention in the liver, and aside from fluid blood in the general peritoneal cavity, there were no noteworthy abnormalities. The thorax, the neck, the floor of the mouth and the brain were not removed for examination.

CONCLUSION

This condition might be suspected in the presence of an enlarging tumor of the right upper part of the abdomen in a young female patient with jaundice. The condition, however, does occur in young male patients and middle-aged persons of both sexes and may not be associated with jaundice. The surgical treatment should depend on the findings in the individual case. The literature emphasizes the high mortality rate associated with aspiration alone or excision. Immediate anastomosis with the gastrointestinal tract may be indicated if the cyst is not too large, its identification is positive, and the patient's condition permits of such a procedure. The ill effects of the total absence of bile from the gastrointestinal tract when complete biliary fistula is established by marsupialization can now be partly obviated by the administration of vitamin K and bile salts or desiccated animal bile. Case 1 is the first to be recorded in which treatment with these agents has been carried out. Each of these cases provides an opportunity for the study of human fat absorption in the absence of bile from the gastrointestinal tract. When such a case is encountered, an immediate recourse to the literature is recommended for the recognition and the pursuit of the problems pertinent to this condition. The literature is so lacking in follow-up reports that the late results of anastomosis of these cysts with the gastrointestinal tract are unknown. Those who have performed operation in such cases are urged to report the late follow-up result of their cases.

622 West One Hundred and Sixty-Eighth Street.

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ABSORPTION OF SURGICAL GUT (CATGUT)

II. PEPSIN DIGESTION TESTS FOR EVALUATION OF DURATION OF TENSILE STRENGTH IN THE TISSUES

HILGER PERRY JENKINS, M.D.

AND

LEO S. HRDINA

CHICAGO

The decline in tensile strength of various sizes, types and brands of surgical gut (catgut) in the tissues was reported in a previous communication.¹ A considerable amount of variation was generally observed in the behavior of the different products studied. This report deals with digestion tests in pepsin and the relation of the digestion time in pepsin to the duration of tensile strength of catgut in the tissues.

Kraissl and Meleney² reported an ingenious method of assaying the resistance of catgut by trypsin digestion in vitro. The end point, at which the catgut undergoes complete loss of tensile strength in the digestive solution, is recorded by means of an electric clock. The electric current to the clock is shut off by means of a switch which is thrown by a counterweight when the catgut strand breaks. The digestion time in hours can then be determined from the time the test was started to the time when the clock was shut off.

It is presumed that all manufacturers of surgical gut have some type of digestion test in vitro which is used in attempting to control the absorption time of their products. It is probable that trypsin is the most generally used enzyme for this purpose. Since the publication of the work by Kraissl and Meleney and a subsequent paper by Kraissl,³ several manufacturers have utilized this method or a modification thereof.

From the Department of Surgery, the University of Chicago, the School of Medicine.

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1. Jenkins, H. P., and Hrdina, L. S.: Absorption of Surgical Gut (Catgut): I. Decline in Tensile Strength in the Tissues, *Arch. Surg.* **44**:881 (May) 1942.

2. Kraissl, C. J., and Meleney, F. L.: A Method for Determining the Time of Catgut Digestion in Vitro, *Surg., Gynec. & Obst.* **59**:161, 1934.

3. Kraissl, C. J.: Intrinsic Factors Altering the Absorption of Catgut, *Surg., Gynec. & Obst.* **63**:561, 1936.

It is of interest to note that Claudius⁴ in 1912 reported the use of pepsin and hydrochloric acid in an attempt to evaluate the absorbability of different kinds of catgut.

Because of the unpredictable behavior in the tissues of different sorts of surgical gut, notwithstanding the rather specific labels customarily used by manufacturers in the past, there appeared to be a place for further work in the field of digestion tests for catgut. Rather than pursue a course which was already being followed by Kraissl and Meleney in their trypsin digestion tests, it appeared desirable to explore the possibilities of another enzyme, such as pepsin, to ascertain whether this might offer a satisfactory basis for evaluating the absorption qualities of surgical gut.

METHODS AND MATERIALS

30 Gm. Tension Pepsin Digestion Test.—After the apparatus designed by Kraissl and Meleney for their trypsin digestion test of catgut in vitro had been inspected, a similar type of apparatus was devised. This consisted of a small incubator in the top of which several holes were bored. A large glass jar to contain the digestive solution was placed in the incubator. The catgut strands were tied to a glass rod above the jar and then carried down into the jar, where they were held in the solution by passing under another glass rod. From there the catgut strands extended upward through one of the holes in the top of the incubator to be attached by a clasp to a cord running over two pulleys to a 30 Gm. lead weight. This weight maintained a constant tension on the catgut, and when the catgut became digested and broke, the lead weight disconnected an electric switch which controlled the circuit to an electric clock. The apparatus so devised accommodated twelve strands of catgut at one time, each of which was fastened to a cord which broke the circuit to one of the twelve electric clocks. The time at which the clock had been stopped represented the end point of the digestion test for that particular strand of catgut. It was necessary to make observations each night in addition to observations during the day, because if the clock stopped at 7:30 one would not otherwise know whether it was 7:30 a. m. or 7:30 p. m. Kraissl solved this point by installing a set of electric clocks with twenty-four hour dials in his more recent digestion apparatus.

The digestive solution originally used for a limited number of tests was pure gastric juice obtained from dogs. Large quantities of this juice were available because of an experimental study of gastric secretion by Dragstedt and associates.⁵ The desirability of an artificially prepared standard strength solution soon became obvious because of the variations in the digestive action of the different supplies of this gastric juice. Experiments were conducted to ascertain what concentrations of pepsin and hydrochloric acid most nearly approximated the results obtained with pure gastric juice. It was found that 10 Gm. of pepsin (U. S. P.) and 1 cc. of concentrated hydrochloric acid made up to 100 cc. with water gave results most comparable with those obtained by the use of the pure gastric juice. The tem-

4. Claudius, M.: Jodchromkatgut, Deutsche med. Wchnschr. **38**:1050, 1912.

5. Dragstedt, L. R., and Ellis, J. C.: The Fatal Effect of the Total Loss of Gastric Juice, Am. J. Physiol. **93**:407, 1930.

perature of the incubator was maintained at 37 C. Over 1,200 digestion tests were carried out with this acid-pepsin mixture and the apparatus described.

2 Gm. Suspension Pepsin Digestion Test.—A relatively simple method of testing catgut in vitro was devised which presented certain advantages over the more elaborate method requiring the use of electric clocks. A standard 100 cc. glass cylindric graduate $9\frac{1}{2}$ inches (24 cm.) in height and 1 inch (2.5 cm.) in diameter was used. A small split lead shot, such as one uses on a fishing line, was attached to one end of a 10 inch (25.4 cm.) length of catgut by forcefully closing the split shot on the catgut strand. The weight of this lead shot was approximately 2 Gm. The catgut strand was lowered into the glass cylinder until the top of the lead shot was at a level with the 10 cc. mark on the graduate. The upper end of the catgut was fastened to the neck of the glass cylinder by a strip of adhesive tape. The digestive solution was warmed to body temperature and poured into the glass container, 110 cc. of solution being used. Any shrinkage of the catgut could then be measured in terms of percentage of the original length submerged in the solution by reading from the graduate the level of the lead shot as compared with its original level at the 10 cc. mark. For example, if the lead shot was sighted at the 30 cc. mark on the graduate after several hours in the solution this represented 20 per cent shrinkage. Observations of shrinkage and subsequent stretching of the catgut during the course of digestion were considered important aspects of the test. The end point was considered to be the time when the catgut was sufficiently digested to break and permit the lead shot to drop to the bottom of the glass. The digestion time in hours was computed from the time the test was started in the incubator until the catgut broke. Four or five strands of catgut were usually placed in one cylinder. It was necessary to use some means of holding the catgut strands away from the glass at the surface level of the digestive solution. This was usually done by a heavy malleable wire which fitted snugly within the neck of the glass graduate above the level of the solution.

The digestive solution used was the same as that mentioned for the 30 Gm. test, i. e., 10 per cent (by weight) pepsin and 0.35 to 0.37 per cent hydrochloric acid (1 cc. concentrated hydrochloric acid to 100 cc. of solution). Readings were made at half-hour to one hour intervals on plain catgut and one to four hour intervals on chromic catgut, depending on the particular product being tested and the stage of digestion. The level of the lead shot attached to each strand was read from the scale on the graduate and recorded so that one would know whether the catgut was undergoing shrinkage or stretching by comparing the data of this observation with previous observations. If one was in the room in which the incubator was installed, one could often detect the sound of the lead weight striking the bottom of the glass as the catgut broke. Many end points were thus accurately recorded. Otherwise the end points were considered to be halfway between the time of the last intact observation and the time when the catgut was found to be broken. It was often necessary to watch these digestion tests throughout the night, although, after becoming familiar with the behavior of the various brands of catgut one could start the tests at a time which permitted observation of the end points at more convenient times. In some instances the glass graduates were placed in an ice box overnight and then replaced in the incubator the following morning. The time spent in the ice box was of course not included in the digestion time recorded for the catgut. This relatively simple method permitted carrying out as many as 100 catgut digestion tests at one time in an ordinary laboratory incubator. The thermostat was set for 37 C. For these tests an incubator with inner glass doors

was used, so that the observations could be made without appreciably disturbing the temperature within the incubator. Approximately 2,000 digestion tests were carried out by this method.

Catgut Tested.—The standard surgical gut of ten different manufacturers was subjected to pepsin digestion tests in vitro. The surgical gut used in these tests was essentially the same as that utilized for tissue implants described in the previous communication. The series of 1937, 1938 and 1939-1940 represent work carried out for the most part during those years on catgut obtained about that time. In the series of 1939-1940, a portion of the same strand of surgical gut used for duplicate tissue implants was subjected to duplicate 2 Gm. suspension digestion tests in pepsin. In the series of 1938, surgical gut obtained from the same lots as those used for tissue implants was checked by the 2 Gm. suspension test. In the series of 1937, the 30 Gm. tension pepsin digestion test was used on surgical gut of similar lots and also on portions of the same strands employed for tissue implants.

The plain, the twenty day or medium chromic and the forty day or extra hard chromic catgut of six manufacturers were tested in sizes from no. 2 to no. 000. This included one product labeled tanned instead of chromic catgut. The twenty day chromic catgut in sizes no. 2, no. 0 and no. 000 of four other companies also was tested. A number of samples of raw unsterilized catgut obtained from several sources were subjected to pepsin digestion. To avoid any misunderstanding regarding the terminology of catgut, it is advisable to review the present method of labeling different types of surgical gut officially adopted by the Committee of Revision of the United States Pharmacopeia.

Official U. S. P. Terminology	Presumably Equivalent Terminology Formerly in Use
Type A: Plain surgical gut (untreated)	Plain catgut
Type B: Mild chromic surgical gut (mild treatment)	Ten day chromic catgut
Type C: Medium chromic surgical gut (medium treatment)	Twenty day chromic catgut; medium hard chromic catgut, ten to twenty day
Type D: Extra chromic surgical gut (prolonged treatment)	Forty day chromic catgut; extra hard chromic catgut, thirty to forty day

The catgut was prepared for the digestion tests by softening in water until it was pliable and then hanging it up to dry with a 35 to 70 Gm. weight tied at one end. Particular care was taken to avoid fracturing the brittle bends in the dry catgut or causing any mechanical damage to the strand. This point has been mentioned by Kraissl as a possible factor in the explanation of discrepancies in digestion tests in trypsin. Even recently opened tubes of nonboilable catgut, which is reasonably pliable, were soaked in water to permit greater pliability before it was stretched out to dry. After the catgut was dry, determinations of the diameter and the tensile strength were made. The catgut was then cut into 10 inch (25.4 cm.) lengths for the 2 Gm. suspension test. Somewhat less than a half standard length of catgut was required for the 30 Gm. tension tests.

RESULTS

Behavior of Catgut in Acid-Pepsin Solution.—During the course of digestion in acid-pepsin solution by the 2 Gm. suspension method, catgut undergoes an original shrinkage phase, an intermediary stationary phase

and, finally, a stretching phase, which is terminated by the breaking of the digested strand. During the first part of the shrinkage phase there may be noticeable evidence of unwinding of the catgut strand, which causes the lead weights to spin around. This may lead to tangling of the several strands in the glass cylinder. Considerable attention is required at the beginning of the digestion test to avoid this difficulty.

The shrinkage observed is undoubtedly due to the acid medium, because comparable amounts of shrinkage occur in the same dilution of acid without the pepsin. The amount of shrinkage bears a relation to the size of the catgut strand, for the larger sizes usually shrink more than the smaller sizes of comparable type. The temperature of the digestive solution affects the magnitude of shrinkage, because in chilled solutions the shrinkage is considerably less. Heat-sterilized catgut undergoes much more shrinkage than the raw product which has not been subjected to heat sterilization.

The rate and the magnitude of shrinkage were found to bear a relation to the length of time required for digestion of the catgut. Those sutures which demonstrated a rapid and considerable shrinkage, of 15 to 30 per cent within an hour or two, were usually found to have a short digestion time, whereas the sutures which showed a slow rate and a lesser magnitude of shrinkage were digested in longer periods of time.

After the phase of shrinkage had gradually reached its maximum, there was a variable intermediary stationary phase before the onset of the stretching phase. The stretching phase undoubtedly represents advanced digestive action of the pepsin on the catgut. The breaking time of the catgut was nearly always during the stretching phase. If the break occurred before the onset of the stretching phase, it was usually found to be due to some local defect in the catgut which caused an apparently greater degree of vulnerability to digestion at this point than was observed for the rest of the strand. In some instances the break did not occur until the strand had regained its original length or had stretched even further. This was observed in some brands of rather thoroughly chromicized fine sutures.

In some of the earlier tests it was found that premature breaking would occur if the catgut strand rested against the side of the glass cylinder at the level of the digestive solution. This can be prevented by the device mentioned, i. e. placing a thick malleable wire ring within the neck of the glass cylinder. Occasionally the lead weights fell off the end of the strand if they had not been properly attached; however, this did not occur more than once in several hundred tests. It was exceedingly rare to find that the breaking point of the strand of catgut was near the place where the lead weight was attached.

When tests were carried out with the use of a small lead weight (2.5 to 5 Gm.) with a wire loop (fishing line sinker) to which the catgut was tied, it was found that plain catgut and certain types of chromic catgut became sufficiently altered by the acid-pepsin solution to cause spontaneous untying of the knots long before the catgut was digested. This untying phenomenon occurred regardless of the care taken in tying a triple throw square knot. This was observed also in pure gastric juice and in gastric contents siphoned from patients after gastrointestinal

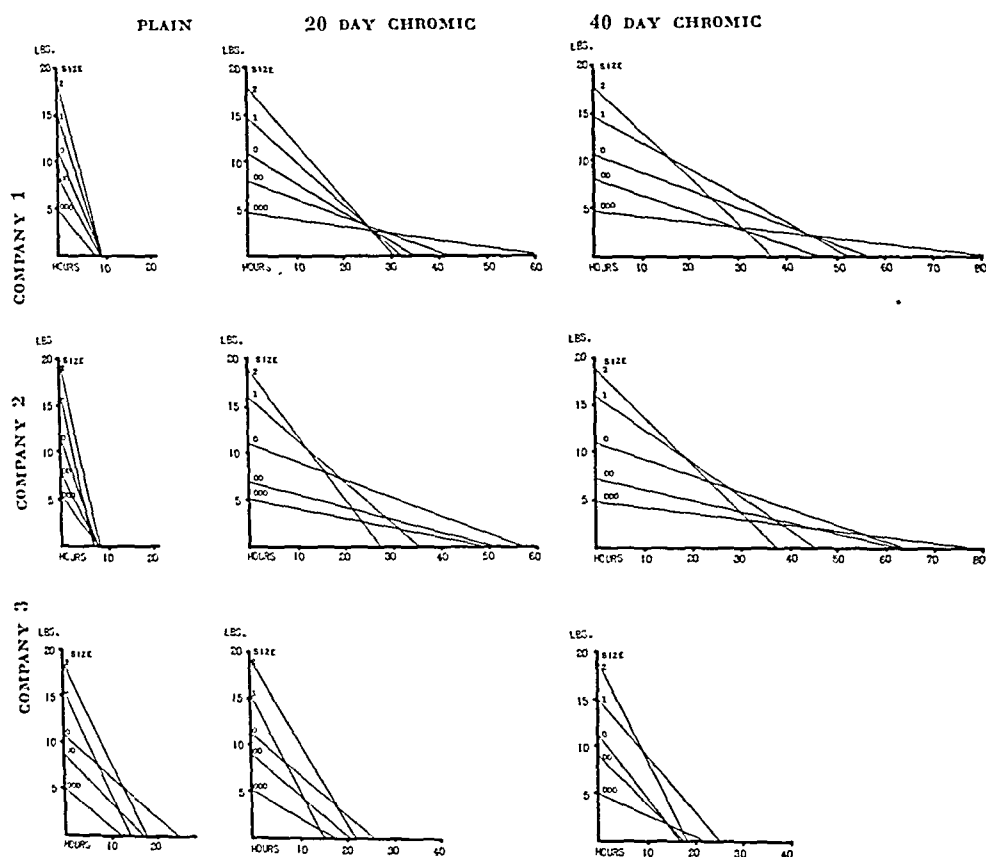


Fig. 1.—Charts showing digestion time of catgut in acid-pepsin solution (series 1939-1940).

anastomosis. The implication of this untying phenomenon in regard to the selection of surgical gut for gastrointestinal anastomosis should be obvious. However, the smaller sizes of the more resistant types of chromic catgut showed almost no tendency to untie spontaneously during the course of acid-pepsin digestion, and, furthermore, it was exceedingly unusual to find that the breaking point occurred at the knot, although it is well known that a knot weakens the tensile strength of catgut by an appreciable amount.

2 Gm. Suspension Pepsin Digestion Tests (figs. 1 to 5; series 1939-1940 and 1938).—In the 2 Gm. suspension pepsin digestion tests, plain catgut was digested within eleven hours on the average, although the digestion time in certain instances was as long as twenty hours or more. The larger sizes of plain catgut showed a tendency to resist digestion longer than smaller sizes, although frequent exceptions to this general tendency were observed.

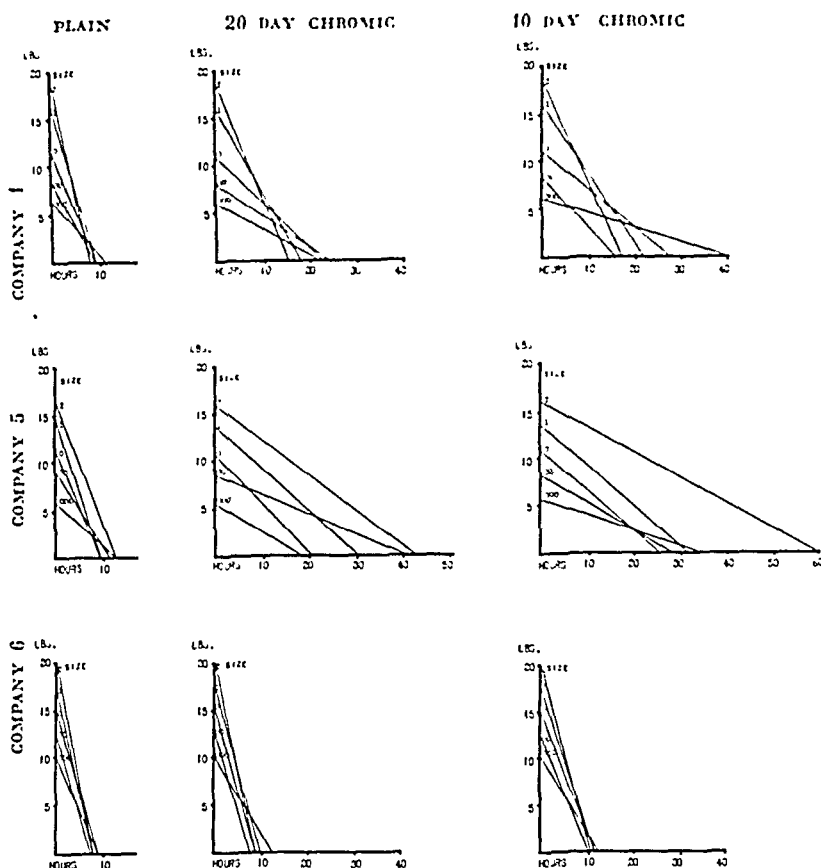


Fig. 2.—Charts showing digestion time of catgut in acid-pepsin solution (series 1939-1940).

The average digestion time of chronic catgut of different manufacturers varied widely. The digestion time of most of the products averaged more than twenty hours, although that for the products of two companies was almost the same as that generally observed for plain catgut. Differences between the twenty day chronic and the forty day chronic catgut of the same company and of the same size were of relatively minor magnitude as compared with the variation in the products of different companies.

In a considerable number of products there was a conspicuous tendency for the smaller sizes of chromic catgut to resist digestion longer than the larger sizes in both the twenty day and the forty day type of surgical gut. In other products the larger sizes frequently held

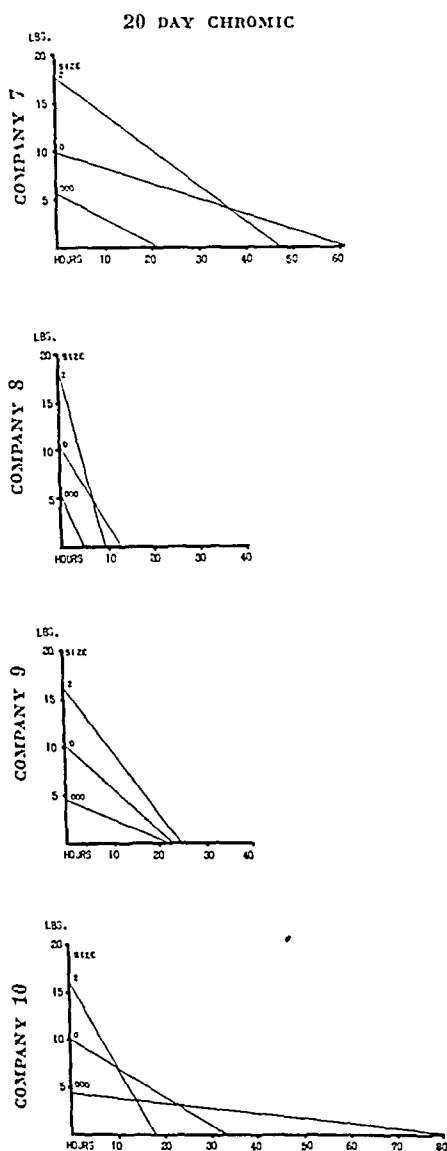


Fig. 3.—Charts showing digestion time of catgut in acid-pepsin solution (series 1939-1940).

up better than the smaller sizes, although in some instances it was difficult to ascertain any special trend in the behavior of the various sizes.

There was a considerable similarity in the behavior of any one product from year to year, although some appreciable differences were observed.

30 Gm. Tension Pepsin Digestion Test (fig. 6; series 1937).—In the 30 Gm. tension pepsin digestion tests, plain catgut was digested in twenty-five to fifty hours, and chromic gut was digested in fifty to one hundred and twenty-five hours or more. The conspicuously longer digestion time by this method was apparently due to maintaining the catgut at a constant tension of 30 Gm. instead of the 2 Gm. used for the suspension test. Experiments involving the use of different weights on

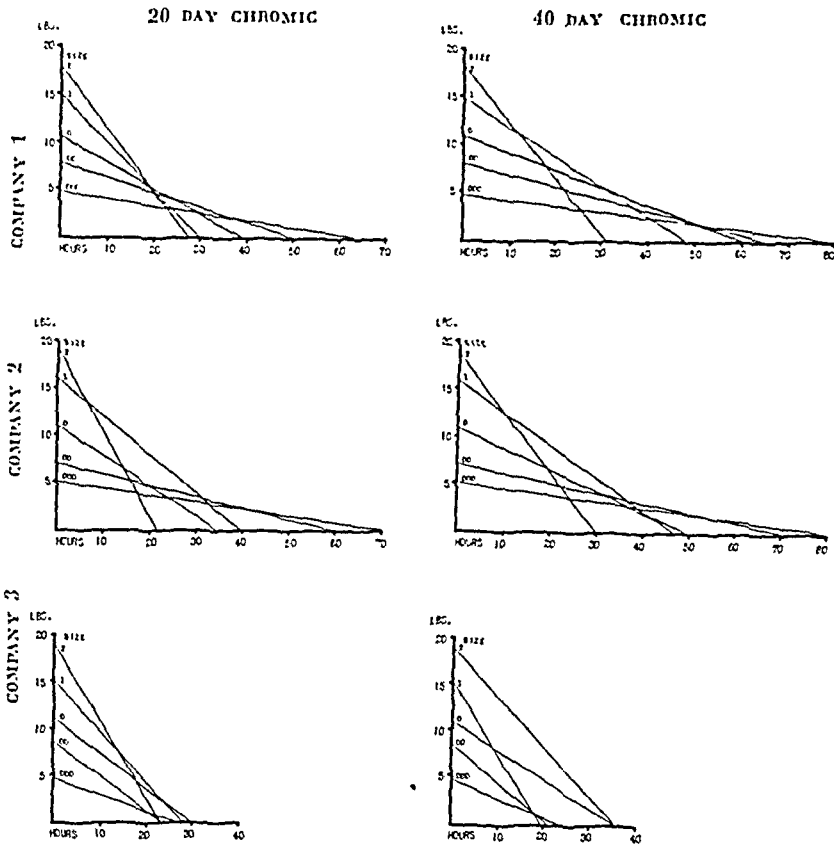


Fig. 4.—Charts showing digestion time of catgut in acid-pepsin solution (series 1938).

portions of the same strand of catgut suspended in the same solution demonstrated that the difference in digestion time was due to the difference in the degree of tension under which the catgut was subjected to the digestive solution rather than to any variation in the potency of the pepsin. The greater tension on the catgut strand subjected to pepsin digestion appeared to delay the penetration of the peptic ferment, and a longer digestion time was the result.

For purposes of comparison of the results obtained by the 30 Gm. tension tests and the 2 Gm. suspension tests, it was found that an approximate relation of $2\frac{1}{2}:1$ existed between the digestion times obtained by these two methods. The charts showing the digestion time in pepsin by the 30 Gm. tension test were made up in such a way that the unit for designating twenty-five hours by this method was the same as was used for indicating ten hours by the 2 Gm. suspension method.

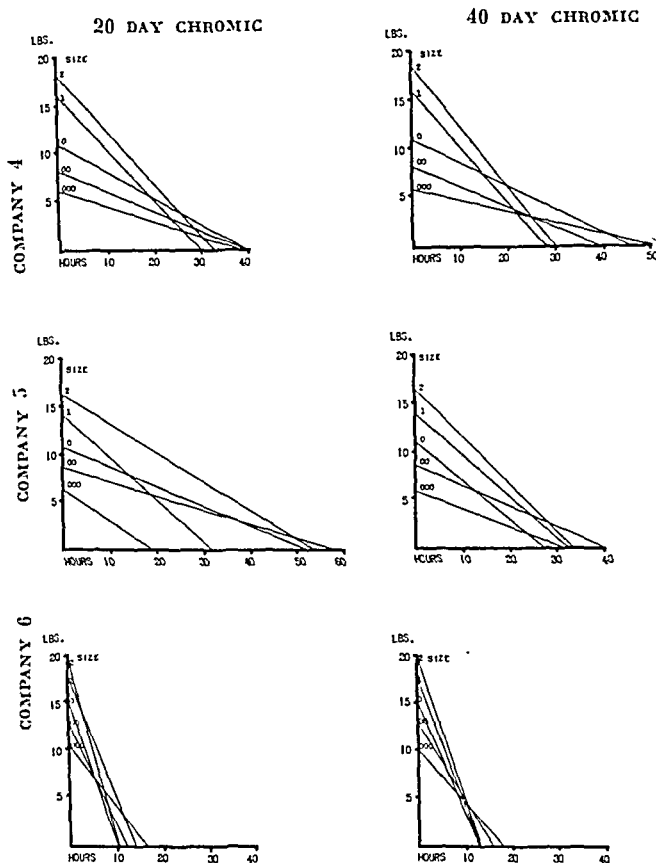


Fig. 5.—Charts showing digestion time of catgut in acid-pepsin solution (series 1938).

Thus fifty hours was equivalent to twenty hours by the 2 Gm. method, and one hundred hours was expressed by the same unit that designated forty hours by the latter test.

With this relation established, it will be found that the general pattern of behavior of the various kinds of surgical gut tested in the series of 1937 was to a considerable extent comparable to the observations made on the other series in which the 2 Gm. suspension method was used. There was, however, a tendency for the various types of

plain catgut to hold up slightly longer in the pepsin under 30 Gm. tension than might be expected if the ratio of $2\frac{1}{2}:1$ is an approximation of the relation in view of the observations generally made by the 2 Gm. tests in the series of 1939. On the other hand, it will be observed that the plain catgut in the series of 1937 may have been somewhat more resistant to digestion because of the slightly longer duration of tensile strength in the tissues observed for this series as compared with the 1939-1940 series.

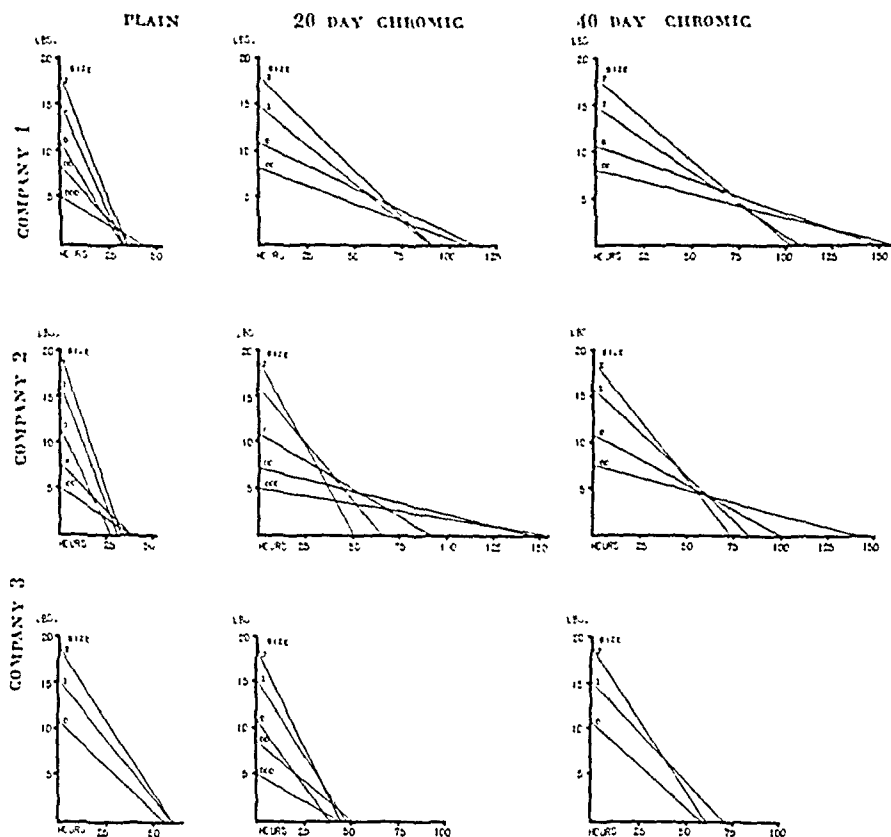


Fig. 6.—Charts showing digestion time of catgut in acid-pepsin solution (series 1937).

The shrinkage and the unwinding phenomena described previously were observed also in tests made with the 30 Gm. tension method but were of less magnitude than in the 2 Gm. suspension test. In some instances these phenomena caused difficulties in the digestion apparatus, which, however, could be easily remedied by attention to the apparatus during the earlier phases of the digestion tests.

Raw catgut which had not been heat sterilized was found to have a rather wide range of variation in digestion time in pepsin. Plain

unsterilized catgut was digested in three to ninety hours by the 30 Gm. tension method and in one and a quarter to thirty hours by the 2 Gm. suspension method, depending on the source from which it was obtained. Chromicized catgut which had not been heat sterilized was found to have a somewhat longer digestion time than was usually observed for the heat-sterilized product of that particular company.

RELATION OF DIGESTION TIME IN PEPSIN TO DURATION OF TENSILE STRENGTH IN THE TISSUES

The method of computing the relation between digestion time in pepsin and the duration of tensile strength in the tissues was as follows: The products of companies 1 to 6 were used for this comparison because these products represented the bulk of the observations made. The series of 1938 and 1939-1940 were taken because the 2 Gm. suspension method was used in these two series. The average digestion time of the plain catgut of all six companies was computed from 350 tests. The average digestion time of the chromic catgut of each of the six companies was determined from a total of 1,190 tests. The minimum number of tests entering into the average for any one company was not less than 150. The tests of twenty day chromic and forty day chromic catgut were averaged together. The various sizes of catgut from no. 2 to no. 000 were equally represented in the averages. The average duration of tensile strength as determined by implants in the abdominal muscles of dogs (reported previously) was computed for these same products. The average duration of the tensile strength of plain catgut was determined from 303 observations, while that for chromic catgut of each of the companies was made from a total of 925 implants. These digestion tests were made on portions of the same strand of catgut or on catgut from the same lots that were used for implants in the tissues.

When the results were plotted on a graph, using the vertical coordinates for digestion time in pepsin and the horizontal coordinates for the duration of tensile strength in the tissues, it was found that the various points were generally falling along a straight line except the point for the chromic catgut of company 2 (fig. 7). It is probable that the relation denoted in the graph is more of a curved line, as indicated on the graph by the interrupted line, because pepsin does undergo some deterioration in its digestive action during the course of the tests. However, for purposes of charting the results on digestion tests as compared with the duration of tensile strength in the tissues, the straight line relation will be considered a reasonable approximation of the situation. On this basis ten hours in digestion time will be considered as approximately equivalent to five days' duration of tensile strength in the tissues, or a ratio of two hours to one day.

The charts showing the digestion time in pepsin are made up in such a way that the unit for designating ten hours is the same as that used to designate five days' duration of tensile strength in the tissues in the charts presented previously. Further, the charts are arranged in the same sequence as those showing the results of implants in the tissues to facilitate comparison. In all these charts the vertical coordinates represent tensile strength in pounds. In this way it is possible to visualize the decline in tensile strength of the various sizes of catgut used. Also, one can then ascertain approximately the residual tensile strength of the catgut at any given time in pepsin or in the tissues. Although

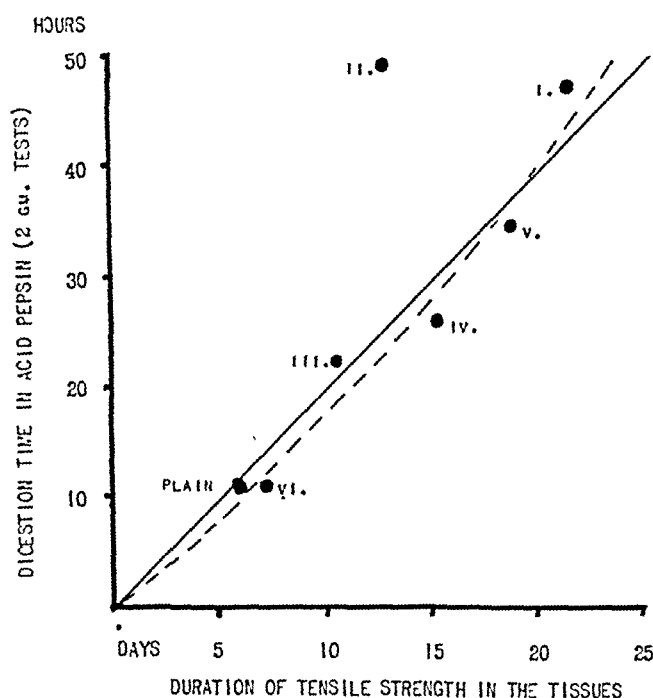


Fig. 7.—Graph showing relation between the digestion time in acid-pepsin solution and the duration of the tensile strength in the tissues of the surgical gut of six manufacturers (companies I to VI). The plain catgut of all companies has been averaged together; the chromic catgut of different companies has been averaged separately. The continuous line represents the approximate relation, i. e., ten hours in acid pepsin is equivalent to about five days in the tissues; the broken line represents the theoretic curve of relation.

the use of a straight line to denote graphically the decline in tensile strength of catgut in the tissues and in pepsin may be open to some criticism, it nevertheless offers a satisfactory method of comparing the relative behavior of the various products in the tissues and in pepsin.

In reviewing the various charts for the several series presented by comparing side to side the general behavior of catgut in pepsin and in

the tissues, the details of the general relationship can be more fully visualized. Although each size of every type of catgut of each of the companies in the three series studied is not invariably identical in its behavior in pepsin and in the tissues, there is nevertheless a comparable trend of behavior for the most part. In view of the fact that the previously reported tests conducted in the tissues are not considered to be more than gross evaluations of the duration of tensile strength, it is surprising to find as much similarity as apparently exists in the various sizes, types and brands of catgut compared.

On the basis of the digestion test one can with some degree of accuracy detect those products or particular sizes of certain products which did not hold up in the tissues for a period of ten days, even though they may have been labeled twenty or forty day catgut, because these usually had a digestion time which was less than twenty hours by the 2 Gm. suspension test. To maintain tensile strength for ten days in the tissues, a treated type (chromic or tanned) of surgical gut should have approximately twice the degree of resistance to digestion possessed by most brands of plain (untreated) catgut.

Also one can ascertain with reasonable accuracy which products have a relatively higher degree of resistance to tissue digestion in the smaller sizes of chromic catgut as compared with the larger sizes, because the digestion time in pepsin is conspicuously longer for the relatively more resistant smaller sizes.

A number of discrepancies of an appreciable magnitude, however, will be noted. In the series of 1939 the plain catgut of company 5 showed a greater resistance to tissue digestion than one would have presumed from the results of the pepsin tests. In the same series the plain catgut of company 3 demonstrated a greater resistance to pepsin digestion than was observed in the tissues. Furthermore, the observations on the chromic catgut of company 2 in all series tested showed a relatively higher degree of resistance to pepsin digestion than was observed in the tissues. In these instances the ratio of digestion time in pepsin as compared with duration of tensile strength in the tissues did not follow the general relationship established for most of the catgut studied which was expressed in the ratio of two hours to one day.

It is rather difficult to explain the discrepancies which have been noted. There are probably a number of factors to be considered, such as the management of the raw product, the duration and temperature of heat sterilization and the chemical agents in the tubing fluid, as well as details in the method of chromicizing. Most of these factors are obviously beyond the scope of the individual investigator, because to a considerable extent they represent trade secrets. Without recourse to practically every detail in the preparation and manufacture of surgical

gut, it is doubtful whether digestion tests *in vitro* can be considered completely reliable in ascertaining the expected duration of tensile strength in the tissues of all varieties of surgical gut.

One can speculate regarding some of the factors mentioned. A particular method of chromicizing may render catgut resistant to enzyme digestion *in vitro*, but because of some irritating substances in the chromic catgut which cause tissue reaction of appreciable magnitude, the rate of digestion in the tissues of this chromic catgut may become accelerated. The irritation may be the result of chemicals used in the tubing fluid, of chemicals which have not been adequately washed out of the catgut after the chromicizing process, or of so-called unfixed chromic compounds. Another possibility is that the products of digestion of this type of chromic catgut may be more irritating to the tissues than chromic catgut prepared by different methods. The presence of irritating substances may cause considerable tissue reaction with exudation and leukocytic infiltration. This increased tissue reaction could probably hasten the absorption of the catgut in the tissues. If a particular type of chromic catgut does cause more tissue reaction than other types of chromic catgut, it should not be surprising to find that its resistance to pepsin digestion does not bear the same relation to tissue absorption as chromic catgut prepared by other methods.

A factor which may enter into the explanation of the variability of results obtained by digestion tests from time to time on some products is that there may be a fundamental difference in the raw products used in the manufacture of chromic catgut. The wide range of variation in the digestion tests on several sources of raw plain unsterilized catgut indicates that there may be appreciable differences in the inherent resistance of the raw product. Furthermore, there may be differences in the response of various raw products to chromicizing. In spite of careful methods of chromicizing, it is amazing that manufacturers are able to produce a chromic catgut with as much precision as is usually done in view of the variable aspects of the original raw product. It is possible that considerable differences in the original raw product may be responsible for some of the differences in digestion time observed in the same companies' products from one year to the next, although changes in the chromicizing process also have to be considered.

COMMENT

A number of points must be taken into consideration in evaluating the reliability of a digestion test designed to assay the absorption qualities of surgical gut. In the first place, the digestive agent deserves consideration, because of the variation in the potency of commercial preparations of enzymes. In an attempt to *prove* this fact, pepsin was

obtained from one source. For the series of 1939-1940, one large lot was obtained which was adequate for all the tests. Various lots of pepsin used throughout the earlier course of this work did not appear to vary in digestive rate by more than 10 per cent or possibly 15 per cent at the most. Whatever variation did occur from various lots of pepsin was fairly well distributed among the tests on assorted products, because no one product was continuously subjected to tests with a particular lot of pepsin.

The rate of deterioration of the digestive enzyme during the course of the digestion test should be considered. An attenuation of the digestive action due to prolonged incubation would give a longer digestion time than the actual resistance of the catgut would justify. It is probable that the exceedingly long digestion time observed for certain small sizes of chromic catgut was due to some extent to the gradual attenuation of the peptic action. A number of tests were conducted to ascertain whether the rate of peptic digestion was consistent throughout the time generally required to digest most products. Five portions of the same strand of catgut were incubated in the same solution. These were removed at various intervals and hung up to dry. The residual tensile strength was determined. The results were plotted on a graph, and it was found that the decline in tensile strength of catgut in pepsin was reasonably consistent during the first forty hours or so but that after this length of time there were some conflicting observations. It was observed, however, that as the catgut approached the end point of its digestion time there was a slight lag in the rate of digestion; this was denoted in the graphs by a tapering off of the relatively straight line as it approached the base line.

The use of relatively high concentrations of pepsin, such as 10 per cent, appears to minimize the attenuation of the digestive action of this enzyme. Also this concentration results in more rapid digestion than is observed with 2 per cent pepsin. Tests conducted with 2 per cent pepsin were approximately 25 per cent longer than those observed for 10 per cent pepsin when portions of the same strand of catgut were checked.

By using a small weight, such as 2 Gm., instead of 30 Gm. for maintaining tension on the catgut during digestion a considerably more rapid rate of digestion is accomplished. The heavier weight prolongs the digestion time by approximately two and a half times that observed with the smaller weight. This factor of a small weight undoubtedly favors the accuracy of the test by increasing the rate of digestion, thereby permitting the completion of the test on most products before any considerable amount of deterioration of the pepsin occurs.

Theoretic objections to the use of a lead weight suspended in an acid medium might be considered; however, the action of the dilute acid on

the lead was of such negligible magnitude that it appeared to have no practical importance as far as the reliability of the test was concerned.

In regard to the problem of preventing the digestive medium from becoming a culture medium for bacterial growth, as is usually observed in trypsin digestion tests carried on for any moderate length of time without the use of a bacteriostatic agent, it was found that the concentration of acid in the acid-pepsin solution was adequate to prevent any apparent difficulties from the growth of organisms.

Certain features of the 2 Gm. suspension pepsin digestion test appear to increase its reliability over that of a test in which the end point is the only observation made. The rate and magnitude of shrinkage, the duration of the intermediary stationary phase and the behavior of the catgut during the stretching phase before the breaking point is reached offer a means of checking the accuracy of the end point observed. It is probable that some correction factors could be worked out for the various products, based on the shrinkage and stretching phenomena observed, which would increase further the reliability of this test.

Aside from the factors of variation in the potency of the pepsin and in the rate of deterioration of the pepsin, one must consider how accurate this test is as far as any one single strand of catgut is concerned. If the test is precise, then one would expect to find that duplicate or quadruplicate tests on portions of the same strand incubated in the same solution at the same time would give end points which were practically identical. This, however, was infrequently observed, although for the most part the range of variation of the end points was within fairly reasonable bounds. In certain products a wide range of variation was sometimes observed for tests in quadruplicate on portions of the same strand of surgical gut. An extreme example of this was the results obtained on a single strand of no. 0 forty day chronic catgut. Although four portions of the same strand were subjected to digestion in the same solution at the same time, the digestion times observed were twenty-five hours, thirty-six hours, sixty-three hours and seventy-eight hours, respectively. Apparently one half of the strand was twice as resistant to digestion as the other half. One would naturally question the reliability of a test which gave such strikingly different readings on portions of the same strand of catgut. However, in checking over the data on the shrinkage and stretching phenomena it was observed that the two strands which were most rapidly digested had undergone 5 per cent shrinkage at the end of one and a half hours, as compared with 2 per cent shrinkage for the other two strands. At the end of twenty-two and a half hours there was approximately 13 per cent shrinkage in the strands which were first to break as compared with 9 to 9.5 per cent shrinkage in the others. Shortly after this reading the stretching phase

began for those two which were soon to break. The 2 more resistant strands did not reach their maximum shrinkage of 11 to 12 per cent until fifty hours, although the other 2 reached their maximum shrinkage in less than half this time. On the basis of observations such as these it is probable that the results of the digestion test expressed in hours of digestion time were reasonably accurate as far as those particular portions of the same strand were concerned. One cannot escape the conclusion that there are occasionally considerable differences in the degree of resistance of different portions of the same strand of chromic catgut. Whether these differences are due to the method of chromicizing or to the raw product is difficult to ascertain.

Some minor differences in digestion time should be expected in tests on different portions of the same strand because of the variation in the physical properties of different portions of the same strand. One may occasionally find variations of $\frac{2}{1,000}$ inch (0.05 mm.) in the diameter of any one strand at different points, and results of tests of the tensile strength may vary by several pounds. For practical purposes the range of variation of different portions of the same strand of catgut from the standpoint of its physical and absorption qualities is probably of negligible importance in most instances.

The 2 Gm. suspension pepsin digestion test offers a means of evaluating raw catgut before it has been put through any of the processes required to produce the finished surgical gut. The digestion time of the raw product undoubtedly bears some relation to the digestion time of the finished product. Furthermore, sufficient correlation might be established between the unsterilized and the heat-sterilized chromic catgut to offer a basis of evaluating the absorption qualities of the chromic catgut before it is tubed, labeled and heat sterilized. A method of determining the resistance of the chromic catgut before it has reached the stage of a finished labeled product should present obvious advantages to the manufacturer. A lot of chromic catgut which does not meet the specifications for a particular type which it is designed to be labeled can then be reclassified and properly labeled before it reaches the stage of a finished product. Trypsin digestion of catgut which has not been heat sterilized is exceedingly slow. It is doubtful whether trypsin digestion offers a satisfactory method for testing surgical gut before it reaches the stage of the heat-sterilized finished product.

In the endeavor to utilize the results and relations of the digestion tests described here for evaluating the absorption qualities of surgical gut generally, it must not be overlooked that the use of a lot of pepsin which differed appreciably in its digestive potency from that used in these tests could cause some distortion of the digestion time of the catgut tested, thereby negating the relations established with the duration of

tensile strength in the tissues. This difficulty can be overcome to some extent provided that one large source of pepsin is available for all the tests to be conducted. With this pepsin the average digestion time of a wide assortment of plain catgut from six or more companies could be taken as a base point or base unit equivalent to approximately five days' duration of tensile strength in the tissues. Twice this base unit would then be approximately equivalent to ten days in the tissues. The base unit multiplied by 3 would then indicate a suture of fifteen days' duration of tensile strength and multiplied by 4 would suggest twenty days' duration of tensile strength. By the use of a base unit such as the one described, the digestive assay of different preparations of enzymes would not substantially affect the relation of digestion time in pepsin to absorption time in the tissues. It is not unreasonable to expect that chromic catgut designed for the average surgeon should have a resistance to digestion which is at least twice that observed for plain catgut of most manufacturers. This would be approximately the equivalent of a minimum standard of ten days' duration of tensile strength for the type of chromic catgut generally used by most surgeons.

SUMMARY

A method of assaying the resistance of surgical gut (catgut) to digestion has been described as the 2 Gm. suspension pepsin digestion test. This consists of suspending a strand of catgut in a glass cylinder by a 2 Gm. weight and subjecting the catgut to the action of a solution of 0.35 to 0.37 per cent hydrochloric acid and 10 per cent pepsin incubated at 37 C. until the catgut becomes sufficiently digested to break. Also a modification of a digestion test apparatus devised by others has been described.

The digestion time in acid-pepsin solution has been determined for the surgical gut of ten different manufacturers. Most of the products have been studied over a period of three or four years. Approximately 3,200 digestion tests have been made.

By the 2 Gm. suspension test, plain catgut was found to have an average digestion time of about eleven hours, although the tests on certain products lasted twenty hours or more. Chromic catgut was found to have a rather wide range of variation, depending on the size of the catgut and the particular product. The average digestion time of chromic or tanned catgut of most companies was in excess of twenty hours, although the products of two companies were digested in a length of time which approximated the average observed for plain catgut. There were relatively minor differences in the digestion time of the twenty day and forty day chromic catgut (types C and D) of any one

company when similar sizes were compared; however, there was often a conspicuously prolonged digestion time observed for the smaller sizes of chromic catgut of some companies.

The digestion time in pepsin by the 2 Gm. suspension test was correlated with previously reported observations on the decline in tensile strength of catgut in the tissues. It was found that for the most part the digestion time in acid-pepsin solution in hours was approximately twice the number of days' duration of tensile strength in the tissues. Thus a digestion time of ten hours would indicate a surgical gut which might be expected to hold up for five days; twenty hours would indicate ten days' duration of tensile strength; thirty hours would be equivalent to fifteen days in the tissues. Although this relation was found to be moderately accurate for most surgical gut products, there were some discrepancies observed. Furthermore, the relation described would of course be materially influenced by the digestive potency of the pepsin used in duplicating these tests. A method of obviating at least to some extent the factor of variability of the digestive agent has been suggested.

CONCLUSIONS

The 2 Gm. suspension pepsin digestion test described offers a simple and rapid indirect method of evaluating the absorption qualities of surgical gut of most manufacturers within certain limitations.

Discrepancies in the reliability of digestion tests on some products will probably not be fully understood without recourse to information on details of the manufacture of surgical gut which is not generally available to individual investigators.

Any standard method of assaying catgut by digestion tests should be checked from time to time by clinical and experimental tissue implants to avoid misleading interpretations of the absorption qualities of surgical gut of the various manufacturers.

SOLITARY UNICAMERAL BONE CYST

WITH EMPHASIS ON THE ROENTGEN PICTURE, THE PATHOLOGIC
APPEARANCE AND THE PATHOGENESIS

HENRY L. JAFFE, M.D.

AND

LOUIS LICHTENSTEIN, M.D.

NEW YORK

Solitary unicameral bone cyst is properly to be regarded as an independent and distinctive lesion and ought not to be included, as it still rather often is, within the omnibus and unjustifiable category of localized fibrocystic disease of bone. It is a relatively uncommon lesion and manifests itself mainly in childhood and adolescence. Nearly always it develops in the shaft of some one of a few predilected long tubular bones, and, in particular, the upper portion of the humeral shaft accounts for about one half of the localizations. Indeed, throughout this discussion, except when we are referring specifically to other localizations, we will have in mind the cyst as it appears in long bones.

Briefly and generally, the lesion can be described as a fairly large fluid-filled unicameral cavity, located in the interior of the affected bone shaft and delimited by a more or less thinned and expanded shaft cortex the inner surface of which (roughened and sometimes distinctly ridged) is lined by a rather thin membrane of connective tissue from which little material, as a rule, can be curetted away. The cyst usually attains a rather large size before its presence is discovered, and often the occurrence of pathologic fracture within its area first calls attention to its existence. The condition is readily amenable to cure by surgical intervention and occasionally even heals spontaneously after pathologic fracture. The features of solitary unicameral bone cyst which are probably the most difficult to understand are its causation and pathogenesis—questions regarding these have raised much discussion.

SOLITARY UNICAMERAL CYST IN LONG TUBULAR BONES

Age and Sex Incidence and Localization.—As noted, it is in the period between early childhood and adolescence that the great majority of patients first come under observation. Specifically, in our group of 19 cases¹ (verified, except in 1 instance, by operative and anatomic

From the Laboratory Division, the Hospital for Joint Diseases.

1. Since the time of writing, we have studied 3 additional cases. In all 3, the lesion was in the proximal part of a humeral shaft, and all 3 patients were about 9 years of age when the condition began to cause trouble.

findings), 15 patients were between 3 and 14 years of age when the condition first began to give them trouble, and the cases were rather evenly distributed over this age group. The ages of 3 of the remaining 4 patients were 16, 18 and 20 years, respectively, at the time of first observation. Thus only 1 patient was a full-fledged adult at the time when the condition first made itself felt. This patient was a man of 42 whose complaints dated back only five years. There seems to be a definite preponderance of males among the patients; in 14 of our group of 19 cases, the patients were males.

As the name solitary unicameral bone cyst indeed implies, the lesion is limited to a single focus in some one bone. As already pointed out, the most strongly predilected bone site is the proximal portion of the humeral shaft, and in 9 of the 19 cases the lesion was in that site. Next in order is the proximal portion of the femoral shaft; this was affected in 4 of the cases. It is probably safe to state that these two sites will account for about two thirds of the localizations in any representative group of cases. The precise localizations for the remaining one third are likely to show chance variation. In the group we are considering here, of the 6 cases still to be accounted for, the lower femoral shaft was involved in 2, the lower tibial shaft in 1, the upper and lower portions of the ulnar shaft in 1 each, and the upper radial shaft in 1.

Clinical Aspects.—As is generally recognized, the cyst is usually already far advanced in its evolution before its presence is discovered. Indeed, it is often not until some slight trauma, direct or indirect, has been followed by the occurrence of a pathologic fracture that medical aid is sought. Patients who do not have pathologic fracture at the time when the cyst is discovered may still give a history indicating one some time back which healed rapidly. In either case, though inquiry may reveal that the fracture had been preceded by slight recurrent local pain and some stiffness of the neighboring joint, it is remarkable, on the whole, how little difficulty there has usually been before the fracture. This often applies even in the case of involvement of a lower limb bone, but in some cases—particularly those in which the lesion is in the upper portion of a femoral shaft—attention is attracted by a limp. Altogether, when a diagnosis of the condition is made before operation, as it often is, it is usually based on the roentgen findings.

Roentgen Picture.—It is when the cyst is in the upper metaphysis of a humerus (its most common site) that the roentgen findings are most likely to guide one to the correct diagnosis. Likewise, when the cyst is in a femur, these findings not infrequently are of diagnostic aid. In relation to other long bones, the picture is not unlikely to be misinterpreted as representing some other lesion. A characteristic feature

of solitary unicameral cyst of long bones is the location in the shaft of the bone, near or relatively near to an epiphysial cartilage plate. Indeed, in a young subject the cyst rarely (if ever) transgresses the plate so as to be both in the shaft and in the neighboring epiphysis. In fact, extension to the epiphysis was not observed in any of our cases in which fusion of the epiphysis with the affected portion of the shaft had not yet taken place. Even in a case (the patient was a boy of 10) in which the cyst had come to extend through two thirds of the shaft of a humerus, the head of the bone remained unaffected. A cyst developing in a long bone after fusion of the epiphysis with the shaft may be found to involve both part of the shaft and the adjacent epiphysial end of the bone. The only instance of this kind which came under our observation was the case of a man of 42 in whom the cyst was situated in the lower end of a femur, and in this case the roentgen findings by themselves would not have led to the diagnosis of bone cyst.

This practical limitation of solitary bone cyst to the shaft at least helps to differentiate this lesion from giant cell tumor of bone, since in the latter the lesion almost invariably begins in the epiphysial end of the bone, though it may reach the shaft by extension. Further, it also seems worth noting here that the two conditions differ significantly in respect to the age distribution of the patients, solitary bone cyst occurring nearly always before the age of 20 and giant cell tumor nearly always after, as we ^{1a} have already pointed out in another connection.

When in the upper portion of a humeral shaft, the cyst, if seen directly or shortly after an initial infraction or fracture, is commonly found to extend from the immediate vicinity of the epiphysial cartilage plate downward for several inches (fig. 1A). The diameter of the humeral shaft in the affected region may be found slightly expanded over a limited area or uniformly. The regional cortex appears attenuated. The thinning can be seen to have taken place from the medullary surface, which may even appear somewhat scalloped. The periosteal surface of the cortex is generally smooth and presents no obvious evidence of new bone apposition except in the immediate vicinity of the infraction or fracture if the latter is in process of healing. Further, on account of the disappearance of markings of the *substantia spongiosa*, the affected area of the shaft appears rarefied to a greater or lesser degree. In some cases, the rarefied area may appear irregularly trabeculated here and there, the so-called trabeculae actually reflecting the presence of ridges on the medullary surface of the modified cortex rather than walls traversing and dividing the cyst.

The initial cortical infraction or fracture line is usually in the proximal portion of the cystic area. The line may be transverse or oblique,

1a. Jaffe, H. L.; Lichtenstein, L., and Portis, R. B.: Giant Cell Tumor of Bone, *Arch. Path.* **30**:993 (Nov.) 1940.

but in any case, even if there is complete severance of continuity, this is not likely to be associated with significant displacement at the site of the fracture. The fracture tends to heal rapidly, and within a month or so continuity has usually been completely reestablished, and only a ridge in the cortex may mark the site of the previous fracture line.

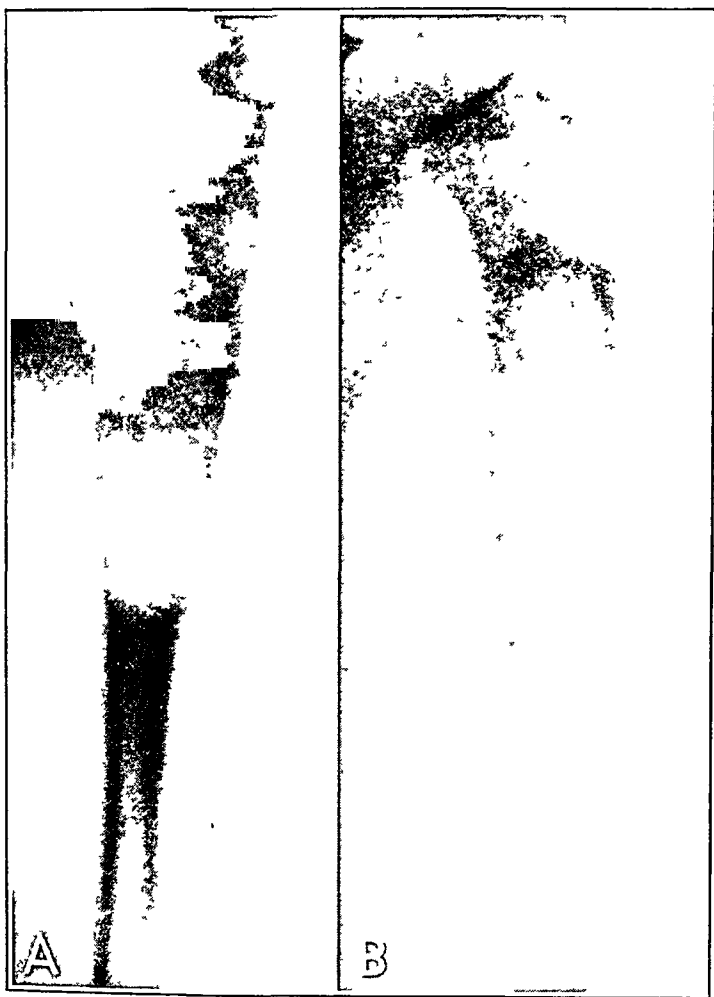


Fig. 1.—Roentgenograms of a cyst occupying a substantial portion of the upper end of a humeral shaft: *A*, taken shortly after the patient had sustained the fracture shown. As can be seen, the rarefaction shadow representing the cyst is not trabeculated and extends downward from the immediate vicinity of the upper epiphyseal cartilage plate. This and the other pictures pertinent to this case were placed at our disposal by Dr. H. D. Sonnenschein. *B*, taken eleven months later. Note that between the epiphyseal cartilage plate and the present upper level of the cyst (the level corresponds in a general way to the site of the original fracture) a portion of the cyst has been obliterated and replaced by reconstructed metaphysis. The cyst has thus passed into its latent phase, out of the active phase shown in *A*.

Sometimes within two or three months after the first fracture one can note that the cystic area proximal to the fracture line is largely filled in with spongy bone, so that the upper limit of the cyst is now as much as an inch (2.5 cm.) below the epiphysial cartilage plate. If this process has not taken place after an initial fracture, it is common, though not inevitable, for it to follow after a second fracture has occurred, most often some months after the first and usually again through the proximal portion of the cyst.

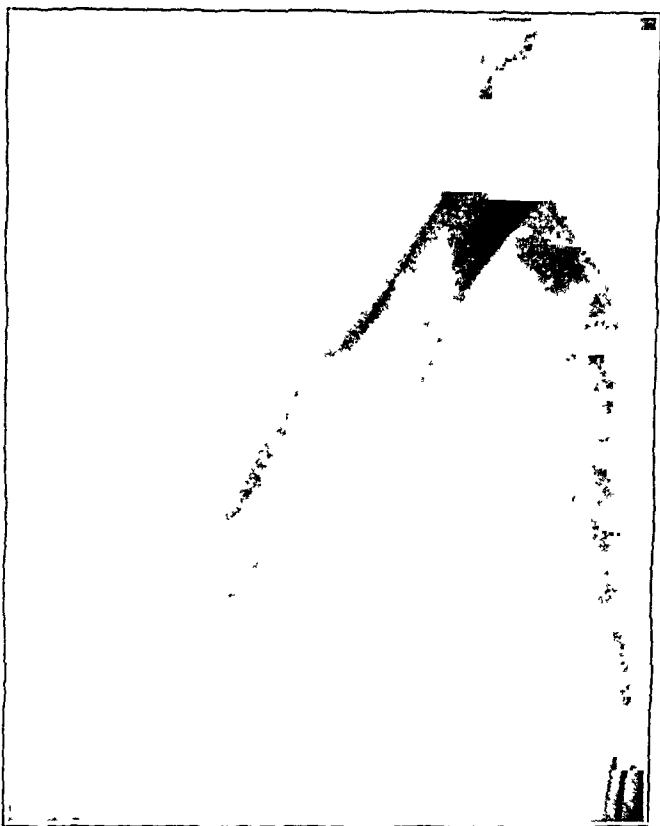


Fig. 2.—Roentgenogram of a cyst occupying the middle of a humeral shaft, the upper limit of the cyst being 3 inches (7.6 cm.) from the plate. Originally (four and a half years earlier), the upper limit had been near the plate. After a fracture then, the cyst passed from an active into a latent phase and gradually moved down the shaft. At the time of writing, it has been in a latent phase for at least four years (as intervening roentgenograms show). However, it did not undergo spontaneous healing or obliteration, even though there had been a second fracture through it ten months before this roentgenogram had been taken, i. e., when the cyst had already been in its latent stage for a long time.

Thus, within a year after the first or even less time after the second fracture, an inch (2.5 cm.) or more of reconstructed metaphysis may be present between the plate and the upper end of the cyst (fig. 1 *B*). At the same time, the longitudinal axis of the cyst may be found

reduced but is not necessarily so, since the cyst may have progressed somewhat at its distal end. In time, in consequence of growth of the bone and reconstruction of the metaphysis between the upper end of the cyst and the plate, the cyst may move a considerable distance down the shaft. Indeed, in 1 of the cases, four and a half years after the initial fracture, the proximal end of the cyst was 3 inches (7.6 cm.) from the plate (fig. 2).

Should there be no such filling in of the metaphysis after a succession of fractures, the cyst usually shows additional progression and may come to occupy a substantial portion of the shaft. In one of the cases—that of a boy of 16 who had had a series of fractures (the first occurring at the age of 11)—the cyst occupied almost all of the upper half of the humeral shaft. In another case—that of a boy of 10—the cyst came to occupy the upper two thirds of the humeral shaft. In this case, the growth of the bone was retarded, the affected humerus being several inches shorter than the one on the opposite side, apparently because during a long part of the period of active growth of the bone, the cyst did not move away from the plate (fig. 3).

A cyst in the upper end of a femur, observed directly or shortly after an initial fracture, is likely to be found extending from the vicinity of the plate belonging to the head into the neck and onward somewhat beyond the trochanters and thus also to have a long axis of several inches. In a case in which a few months have elapsed between the fracture and the roentgen examination, one may find that much of the neck has been reconstructed, and the cyst may even be situated between and below the trochanters. On the other hand, if, on account of pain and limp, the patient came under observation before fracture has occurred, the upper end of the cyst may even still be abutting on the plate. In the lower femoral shaft of a patient who is still a youth and presents a history of fracture some months before, it is likely to be found that the cyst has moved upward from the plate. Altogether, cysts of the femur (whether in the upper or the lower portion of the shaft) tend to present essentially the same roentgen picture as those in the upper part of the humeral shaft, though the picture is not so characteristic as when the lesion is in the latter site.^{1b}

1b. Not directly pertinent to the lesion under discussion, but of interest in connection with the general question of cystlike rarefactions in bone are the cystlike areas observed by Sontag and Pyle (Sontag, L. W., and Pyle, S. I.: The Appearance and Nature of Cyst-Like Areas in Distal Femoral Metaphyses of Children, *Am. J. Roentgenol.* 46:185, 1941) rather frequently in girls and more frequently in boys in the course of serial skeletal examinations of normal children. Specifically, they found small cystlike rarefactions, somewhere between 0.5 and 1.5 cm. in diameter, on the medial aspect of one or both lower femoral metaphyses in the cases in question. The rarefactions were completely asymptomatic, were usually already present by about 4 years of age and usually disappeared spontaneously within the following two years.

In other long bones, the cyst, when first observed, is not uncommonly found to have moved several inches away from the neighboring plate. Thus a boy of 16 having a cyst in the upper part of a radial shaft showed the cyst beginning $2\frac{1}{2}$ inches (6.35 cm.) below the plate

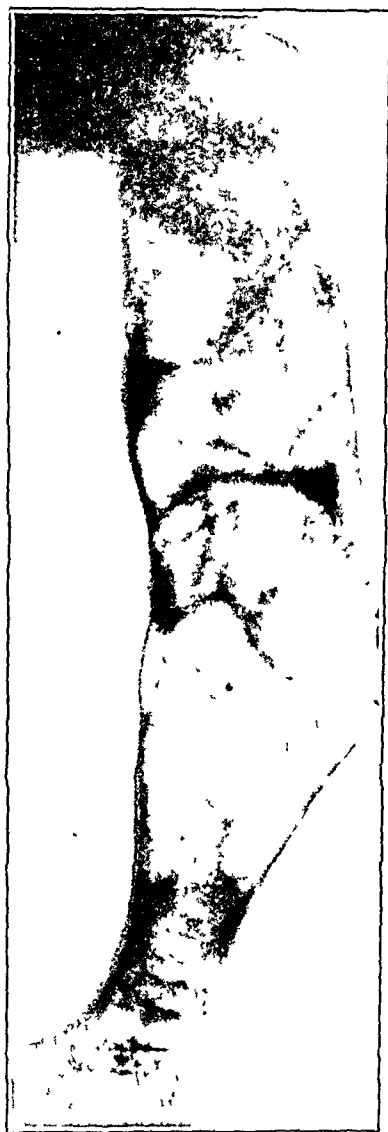


Fig. 3.—Roentgenogram of a cyst which, because it remained in an active phase, came to occupy fully two thirds of a humeral shaft. The affected portion of the shaft was found to be represented merely by a thin, and in places even parchment-like, somewhat ridged cortical shell enclosing a fluid-filled cavity from the wall of which only a few curet spoons of material could be obtained. This picture and the other one pertinent to this case were placed at our disposal by Dr. Henry Milch.

of the head and extending 3 inches (7.6 cm.) down the shaft. In a girl of 14 whose cyst was in the lower part of an ulnar shaft, it began $1\frac{1}{2}$ inches (3.8 cm.) from the plate and extended $1\frac{1}{2}$ inches up the shaft. In a girl of 10 whose cyst was in the lower part of a tibial shaft, it began 2 inches (5 cm.) from the plate and extended $2\frac{1}{2}$ inches (6.35 cm.) up the shaft. On the other hand, in a boy of 8 having pain and disability at the elbow of only two weeks' duration, the cyst was smallish, extending from just below the coronoid process of the ulna downward for only an inch (2.5 cm.). In 2 of these 4 cases in which the cyst was in some long bone other than a humerus or a femur, the cyst did not even extend across the entire width of the affected part of the bone. Further, in none of the cases could one be reasonably certain on the basis of the roentgen picture alone that one was dealing with a cyst (fig. 4 *A* and *B*). In particular, the roentgen picture presented by these lesions of long bones could not readily be distinguished from that seen in certain cases of solitary fibroma (osteogenic or nonosteogenic) or enchondroma or in connection with a localized focus of fibrous dysplasia.²

Pathologic Appearance.—In the course of exposing the cyst, the surgeon finds the overlying muscles unaltered, unless there has been a recent fracture, in which case they are likely to be discolored from hemorrhage. When the muscles are retracted, the cortical wall of the cyst may present a bluish sheen, apparent even through the periosteum, accounted for by the thinness of the cortex and its consequent translucency to the fluid in the cyst. Indeed, in some places the cyst wall may be of almost eggshell thinness. When the periosteum is stripped off, it may be found that where the cortex is especially attenuated, parts of the latter may even show tiny defects. The fluid which is evacuated when the cortex is cut through may be clear and yellowish or else serosanguineous. If there has been a recent fracture through the cyst, the fluid is likely to be heavily discolored by blood, and the cyst may even contain coagula of blood. In only 1 of our cases (that of a smallish lesion in the upper metaphysis of the ulna) did it appear from the surgeon's note that there was no fluid in the cyst.

On evacuation of the fluid and exploration of the cavity, the latter is found not to be divided off into compartments. However, the inner wall of the cortex may show some meager bony ridging, and in an occasional case a few projections may be found jutting prominently into the cavity. Further study commonly shows that the inner surface of the cortex is lined by a connective tissue membrane which, most often, is smooth and thin. If the fluid content was not frankly sanguineous, the basic color of the membrane will be gray white, though

2. Lichtenstein, L.: Polyostotic Fibrous Dysplasia, Arch. Surg. 36:874 (May) 1938.

patches of it may show rust brown discoloration. If one curets the inner wall of a cyst, it is striking to find how little tissue can usually be obtained. A cyst several inches in length may yield only 2 or 3 curet spoons of material. Occasionally, however (as was shown in 2 of our lesions, each in the lower end of a femur), a considerable amount of yellowish and brownish material, obviously containing a good deal of lipoid, could be curetted from a few places on the cyst wall.

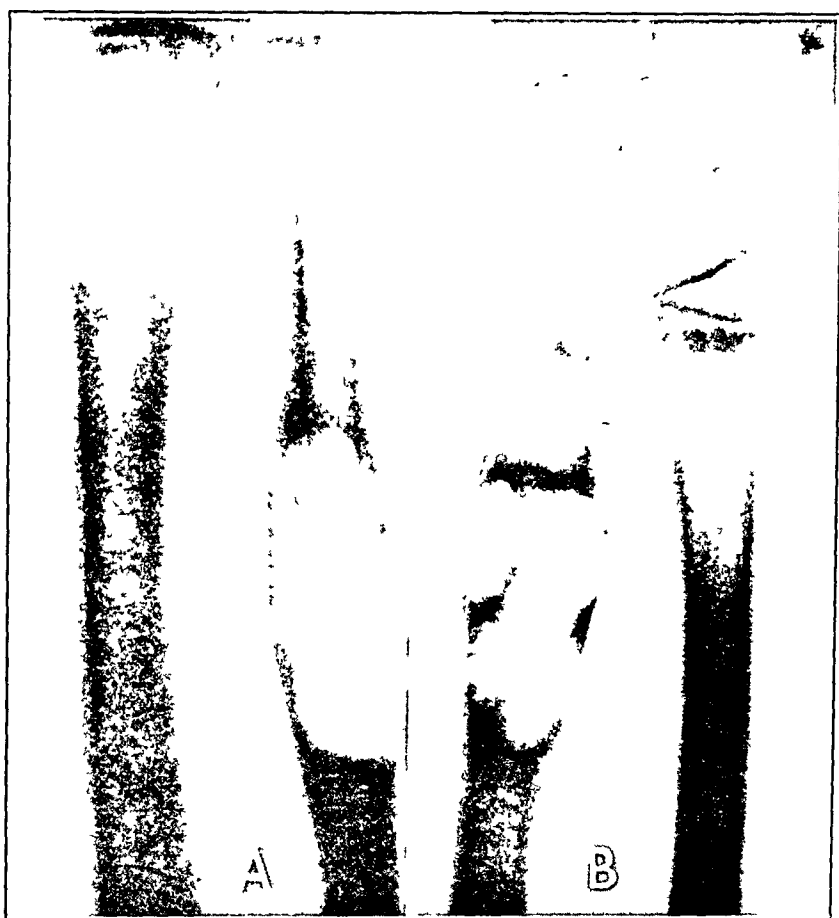


Fig. 4.—*A*, roentgenogram of a solitary unicameral cyst in the shaft of an ulna. The cyst is in a latent phase, and its distal end is about $1\frac{1}{2}$ inches (38 cm.) from the distal plate. For this picture we are indebted to Dr. Samuel Kleinberg. *B*, roentgenogram of a nonosteogenic fibroma of an ulnar shaft. In this case, the area in question was found completely filled with firm brownish fibrous tissue consisting histologically of whorled bundles of spindle connective tissue cells moderately interspersed with smallish, often elongated, multinuclear giant cells. From the roentgenogram alone, one could not have been at all certain that one was not dealing with a cyst in this case too. For this picture we are indebted to Dr. Isaac Reitzfeld.

On microscopic examination, the thin cortical wall of the cyst is found composed of rather loose-meshed osseous tissue (fig. 5). This represents a new cortex which has slowly been laid down by the periosteum as the old cortex was being resorbed. It is only at sites of infraction that obvious signs of active periosteal new bone apposition are present. The fairly large vascular spaces of the cortical shell usually show many dilated and thin-walled vessels. On the walls of these spaces, a scattering of osteoclasts may be seen, and some osteoclasts

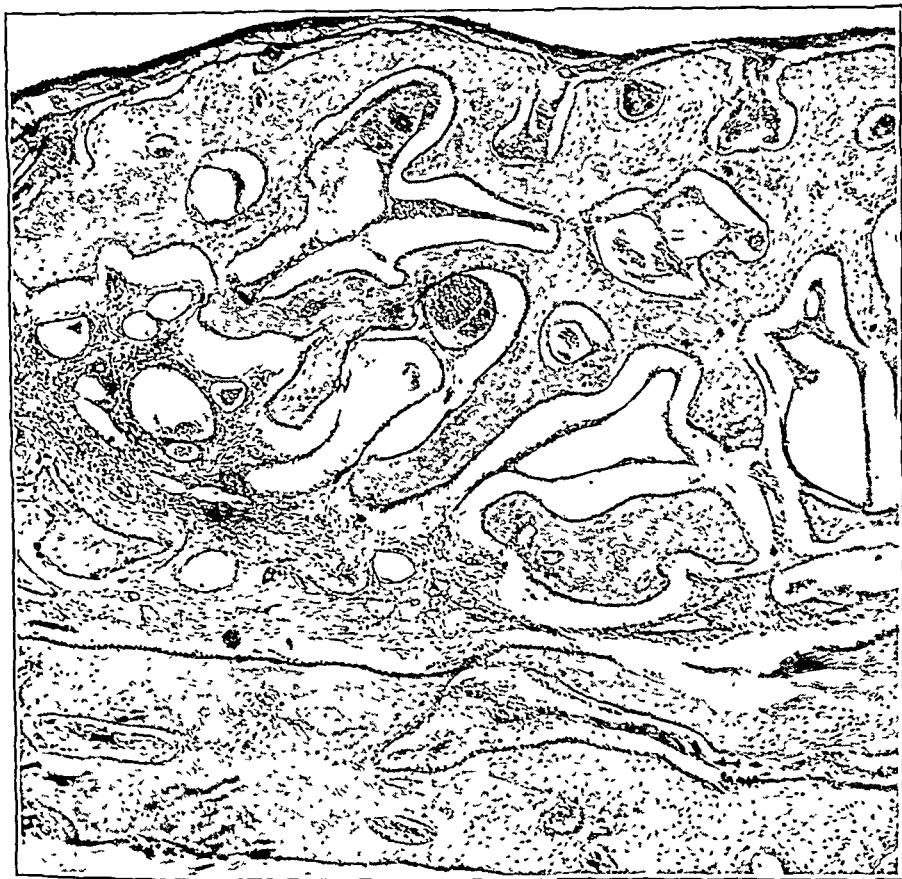


Fig. 5.—Photomicrograph ($\times 30$) showing the histologic details at one point in the cortical shell of the cyst pictured in figure 3. In the area in question, the cortex was not nearly as thin as it was, on the whole, elsewhere. The lining of the inner surface of the cortex (upper margin in the picture) is a mere membrane of connective tissue. Below it can be seen the osseous tissue, permeated by large spaces containing vessels. At the lower margin of the picture, the outer surface of the cortex can be seen, devoid of periosteum, which had been stripped away at the operation.

may be present also between the periosteum and the outer surface of the cortical shell on the one hand and between its inner surface and lining membrane on the other.

As noted, this membrane is thin in most places, consisting in these of only a few superposed layers of connective tissue cells. In other places, the membrane may be slightly thicker and be composed essentially of rather vascular connective tissue. It may also show a scattering of blood pigment, either free or within phagocytes. Here and there in the lining membrane, some osteoid and osseous trabeculae may be seen to have formed through metaplasia. The bits of tissue which are usually found adherent to the lining of the cyst will appear on microscopic

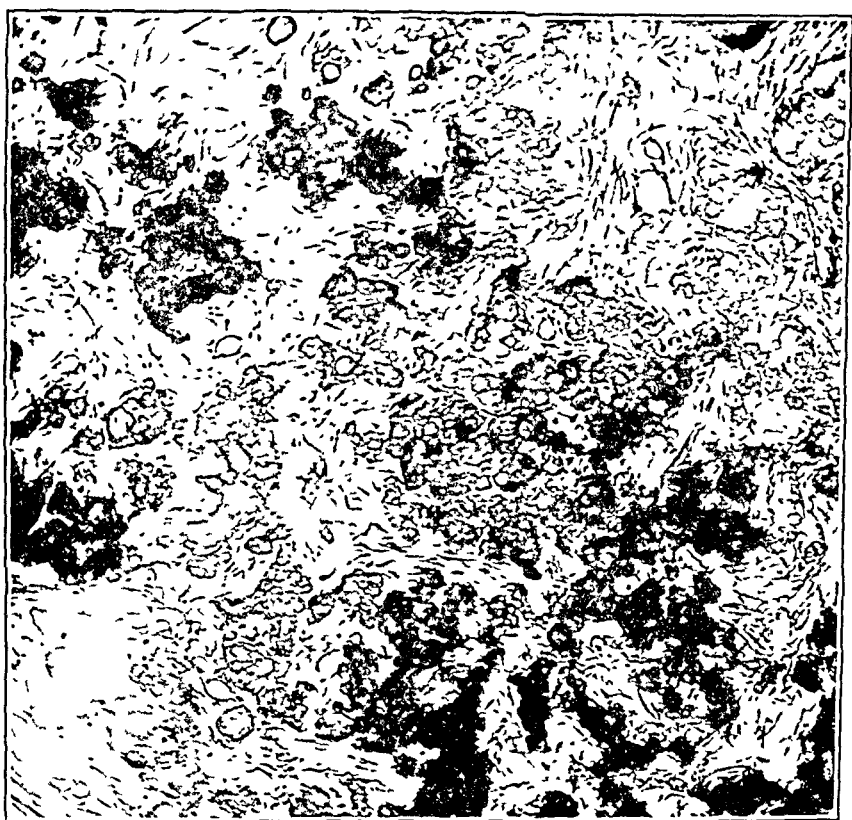


Fig. 6—Photomicrograph ($\times 115$) showing the histology of the bits of organizing and calcifying fibrin and blood clot which are not infrequently curetted from the wall of a cyst. The agglutinated masses of fibrin and red blood cells are enmeshed in a moderately vascularized substratum of delicate connective tissue cells. The darkest areas represent those in which the calcification is most intense

examination to be mainly fibrin clots, often containing some red blood cells and undergoing organization and even calcification and ossification (fig. 6). In 1 of the 2 cases mentioned in which a relatively generous amount of brownish material could be curetted from some places on the cyst wall, this material consisted mainly of cholesterol crystals embedded

in fibrin (fig. 7). In the other, the material included crystals, but also foam cells, hemosiderin-bearing phagocytes and many foreign body giant cells. Any substantia spongiosa that may have been removed from beyond the immediate limits of the cyst is likely to show remodeled trabeculae, while the intertrabecular marrow appears mucoid or fibrous and contains thin and dilated blood vessels.

Causation and Pathogenesis.—At least before the hyperparathyroid basis of Recklinghausen's disease had been demonstrated, some were



Fig. 7.—Photomicrograph ($\times 115$) showing the histology of the brownish material which is occasionally found adherent to the wall of a cyst. Note the spaces representing the shape of cholesterol crystals previously present and the foreign body giant cells about these spaces. Some hemosiderin-containing phagocytes and some lipophages also are present.

willing to assign the same origin to solitary unicameral bone cyst as to the bone cysts in the former disease. Thus, building on the conception held by Engel³ of the bone cysts in Recklinghausen's bone disease,

3. Engel, G.: Ein Fall von cystoïder Entartung des gesammten Skelets, Thesis, Gießen, F. C. Pietsch, 1864.

some authors have interpreted solitary bone cyst as resulting from hemorrhage after vessel tears in an area of bone softening. While not entirely implausible, this theory leaves the hypothetic bone softening undefined and unexplained, and it has been generally discarded. Others, including Recklinghausen⁴ himself and Schmidt,⁵ have conceived of solitary bone cyst as representing simply an area of fibrous osteitis which has undergone cystic degeneration. This theory is rendered highly implausible by the facts that curettement of the wall of a solitary unicameral cyst rarely yields, as has been noted, more than a few tiny fragments of tissue at all, and that on microscopic examination such tissue as can be obtained proves to be mainly fibrin or blood clot in various stages of alteration and not the kind of tissue which one obtains from a cystically softened solitary fibroma or focus of fibrous dysplasia in bone. Running parallel with this fibrous osteitis theory there was the conception, proposed by Virchow,⁶ that solitary bone cyst represents a central bone tumor and in particular some sort of chondromatous lesion which has likewise undergone cystic softening; here again is a conception which lacks basis in fact.

According to another theory, which is still in good favor in some quarters, solitary bone cyst represents a healing form of localized osteitis fibrosa or tumor-forming localized osteitis fibrosa—that is, of so-called giant cell tumor. This idea seems to have been fathered by Mönckeberg,⁷ developed by Konjetzny⁸ and adopted also by Geschickter and Copeland.⁹ It is true that a giant cell tumor may undergo partial cystic degeneration. However, it is difficult to understand why this fact should necessarily lead to the interpretation of solitary bone cyst as a healing form of giant cell tumor. In the first place, as already pointed out, giant cell tumor appears at a definitely later age, on the average, than solitary bone cyst. Further, a giant cell tumor nearly always starts in an epiphysis, while a solitary bone cyst nearly always starts in a metaphysis and only rarely transgresses into the epiphysis. In addi-

4. von Recklinghausen, F.: Die fibröse oder deformierende Ostitis, die Osteomalacie, und die osteoplastische Carzinose in ihren gegenseitigen Beziehungen, in Festschrift Rudolf Virchow zu seinem 71. Geburtstag gewidmet, Berlin, G. Reimer, 1891.

5. Schmidt, M. B.: Allgemeine Pathologie und pathologische Anatomie der Knochen, *Ergebn. d. allg. Path. u. path. Anat.* **7**:221, 1900-1901.

6. Virchow, R.: Ueber die Bildung von Knochenzysten, *Sitzungsb. d. Akad. d. Wissensch.*, Berlin, 1876, p. 369.

7. Mönckeberg: Ueber Cystenbildung bei Ostitis fibrosa, *Verhandl. d. deutsch. path. Gesellsch.* **7**:232, 1904.

8. Konjetzny, G. E.: Die sogenannte "lokalisierte Ostitis fibrosa," *Arch. f. klin. Chir.* **121**:567, 1922.

9. Geschickter, C. F., and Copeland, M. M.: Tumors of Bone, revised ed., New York, American Journal of Cancer, 1936, p. 243.

tion, again as already stated, a solitary cyst usually has few if any tissue masses adherent to its wall, and when they are present their histologic architecture does not correspond to that of a genuine giant cell tumor. The bits of tissue may indeed show, among other elements, a sprinkling of giant cells, especially in relation to areas of hemorrhage, but these cells are not embedded in a stromal tissue of the kind seen in giant cell tumor.^{1a}

A much more cordial reception has been given to the theory advocated by Pommer.¹⁰ According to this theory (based on histologic study of 1 case), solitary bone cyst results from the encapsulation and alteration of a focus of intramedullary hemorrhage. It is thought that after the affected area has been encapsulated, it is kept distended by transudation of fluid into it and that pressure from the cyst causes stagnation in the blood and lymph channels about it, pressure erosion of the neighboring bone and finally even expansion of the overlying cortex. This theory is confronted with the obvious objection that cysts do not follow on fractures, though the latter are, of course, associated with hemorrhage. To meet this objection, the proponents of the Pommer theory (e. g., Lang¹¹) argued that when fracture occurs, the periosteum is torn, and the possibility of developing a closed pressure cyst is removed. Hence it is postulated that it is only after mild trauma without fracture but with intramedullary hemorrhage that bone cysts on a hemorrhagic basis develop.

Mikulicz¹² at least recognized that solitary bone cyst (which he designated osteodystrophia cystica juvenilis) constitutes a disease entity. Further, he held that its predilection for young subjects and for regions of active growth of long bones suggest that it represents some local disturbance in bone growth and development. In fact, he held that it represents a local post-traumatic dystrophy. Mikulicz' conception of the causation of solitary bone cyst has not received general recognition. However, it seems to us that (except for its inclusion of the dubious idea of a traumatic factor as the instigator of the growth disturbance), this conception has much in its favor.

One evolutionary feature of the lesion in question which seems not to have been sufficiently emphasized and which has attracted our attention is that the cyst may pass from an active into a latent phase. Specifically, a cyst which extends to the immediate vicinity of, or abuts

10. Pommer, G.: Zur Kenntnis der progressiven Hämatom- und Phlegmasieveränderungen der Röhrenknochen, *Arch. f. orthop. u. Unfall-Chir.* **17**:17, 1920.

11. Lang, F. J.: Beiträge zu den mikroskopischen Befunden bei Knochenzysten, *Deutsche Ztschr. f. Chir.* **172**:193, 1922.

12. von Mikulicz, J.: Ueber cystische Degeneration der Knochen, *Verhandl. d. Gesellsch. deutsch. Naturforsch. u. Aerzte* **76**:107, 1906.

on, an epiphysial cartilage plate must be regarded as an active one still possessing potentialities for growth. On the other hand, a cyst which has definitely moved away from the plate, so that there is now a reconstructed area of shaft between it and the plate, has entered into the latent stage of its life cycle, for its growth activity has ceased. The lesion may now be regarded as merely a static defect in the bone, though this defect may maintain itself for years and even be the basis for subsequent refrac-

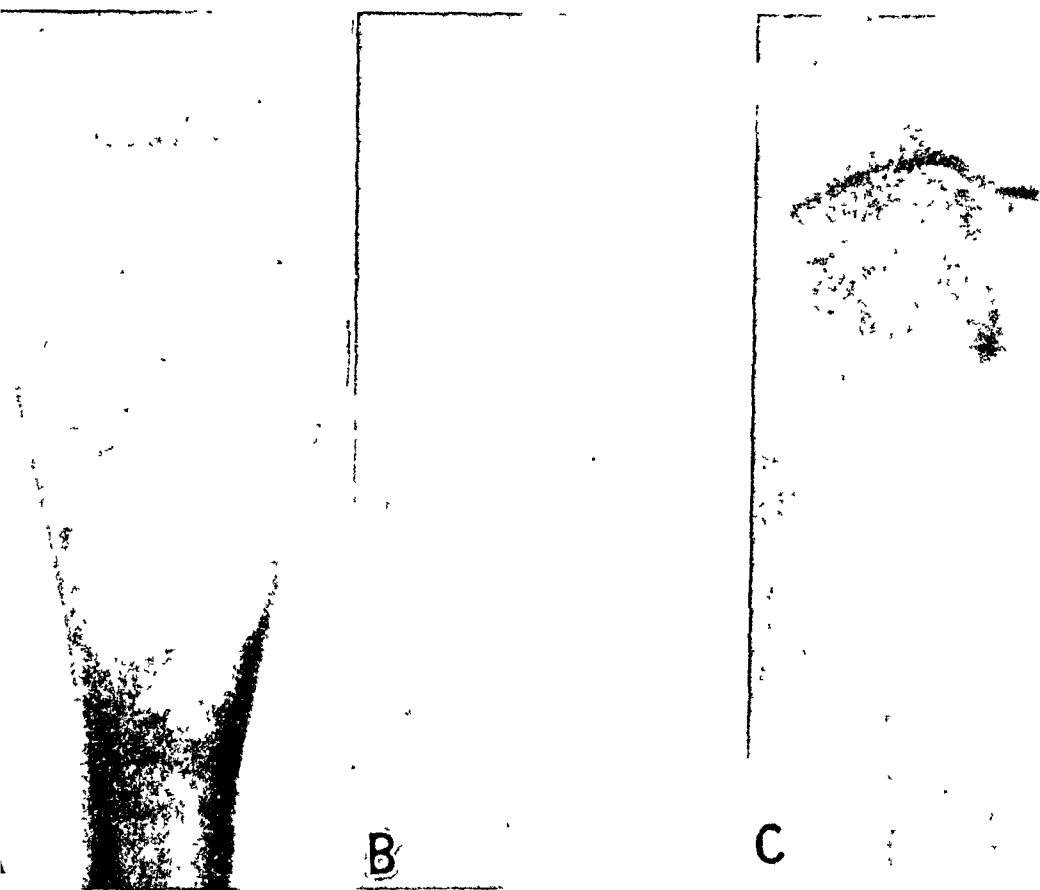


Fig. 8.—*A*, roentgenogram showing a somewhat trabeculated rarefaction shadow representing a cyst in the upper end of the humeral shaft with an infraction in the cortex. This picture was taken ten days after the patient had had a sudden attack of pain while swimming. *B*, roentgenogram showing the appearance of the affected area two months later. Note how opaque this area appears in comparison with what it was. *C*, roentgenogram showing recystification of the area, fourteen months after the picture shown in *A* had been taken. Except for support of the area while the fracture was healing, no treatment other than some baking and massage was given. In a roentgenogram taken six months after the one illustrated in *C*, the appearance was essentially the same.

tures. It is in this latent and static stage that the cysts heal most promptly in response to curettage and filling with autogenous bone chips.

Treatment.—Apparently a solitary bone cyst occasionally becomes spontaneously filled in (after a fracture) as is demonstrated by the course in the case described by Adams.¹³ However, this course is much more exceptional than it has often been thought to be. A cyst of the upper part of the humeral shaft from a case in our series showed what appeared to be spontaneous rapid filling in after an infraction of the cortex from slight trauma. However, fourteen months later, though the cortex of the affected area was now fairly thick, the substantia spongiosa again appeared cystic. Indeed it was now multicystic, as though partitioned off into a number of small cavities. What had apparently occurred was that the lesion had changed from a unicameral cyst with a thin cortex to a multicameral cyst the cortex of which was thick in some places so that although the cyst had not healed in completely, no further clinical difficulty was to be anticipated (fig. 8).

In describing the roentgen picture of bone cyst, it was pointed out that some months after the initial fracture, but more often after the second or third fracture, it will be observed that an area of reconstructed metaphysis is present between the cyst and its neighboring epiphysial cartilage plate. In the discussion of the pathogenesis, it was emphasized that if the cyst has moved away from the neighboring plate, the growth activity of the cyst has ceased, the latter having changed from active to static (figs. 1 *B* and 2), and that static cysts are highly amenable to surgical intervention.

The treatment of choice (whether or not the lesion has moved away from the plate) is to expose the cyst, curet its wall, fill it with autogenous bone chips (e. g., from the tibia), collapse the cyst wall and close the wound tightly. This procedure can be expected to yield a cure in most cases, and indeed it did so promptly in all of our cases in which the cyst was static at the time of surgical intervention (fig. 9 *A*). On the other hand, in 2 cases in which the cyst was still abutting on the plate at the time of operation (1 of the cysts was also heavily radiated before operation), prompt healing did not take place after curettage and introduction of bone chips. In both cases, large cystic areas reappeared, and in both cases pathologic fractures recurred. However, also, in both instances, even without a second surgical intervention, a good deal of healing was subsequently observed (fig. 9 *B*). The course of this could have been expedited by a second intervention, with renewed curettage and refilling with bone chips.

In no case did we find that any benefit resulted from radiation therapy. Certainly this therapy does not favor healing of the cyst

13. Adams, A. W.: Report of a Case of Solitary Fibrocystic Disease of the Humerus Exhibiting Spontaneous Resolution, *Brit. J. Surg.* **13**:734, 1926.

without surgical intervention. On the other hand, when given before or after such intervention, there is at least the theoretic possibility that it may even delay healing.



Fig. 9.—*A*, roentgenogram showing, in a healed condition, the cyst pictured in figure 1 *A* and 1 *B*. This picture was taken only four months after bone chips had been introduced into the cyst, which, as 1 *B* shows, was already in a latent stage. *B*, roentgenogram showing the status of the humeral cyst pictured in figure 3, but four and a fourth years after it had been filled with autogenic chips and slivers of bone. Comparison between the figures reveals the thorough reconstruction which has taken place in the proximal portion of the affected shaft and shows, altogether, that much of the deformity has corrected itself. It is true that the middle of the shaft is still cystic and shows a recent transverse fracture. However, the cyst is now in a latent stage, and there is every indication that rapid and complete healing will take place, especially if the area is again filled with bone chips.

SOLITARY UNICAMERAL CYST IN BONES OTHER THAN LONG
TUBULAR BONES

Our own hospital records from 1925 to date include no case in which a solitary unicameral cyst of a kind entirely analogous to that appearing in long tubular bones was found in some other bone. It is perhaps worth noting, however, that we did encounter, as an incidental finding in a rib, a cyst which, while multicameral at the time of removal, looked as though it might have been a unicameral cyst which had undergone only partial spontaneous healing. Altogether, our experience is not out of harmony with the acknowledged rarity of solitary unicameral bone cyst in other than long tubular bones. Of the supposed instances reported, it is possible that some of those in which the lesion was in a metacarpal or a metatarsal bone shaft actually do represent such cases, since the development and structure of these short tubular bones is parallel to that of the long tubular bones. However, reservations are in place even in regard to these supposed instances. For example, among the cases described by Platt¹⁴ as instances of cyst of the tubular bones of the hand or the foot there are only 1 or 2 that may possibly be such, and even these must be accepted with reservation. The occurrence of this cyst in bones which develop like epiphyses from a single center of ossification (e. g., the astragalus) seems rather unlikely, since the cyst appears to start its development not in epiphyses but instead in a shaft region abutting on an epiphysal cartilage plate.

ANEURYSMAL CYST

Under this heading, we wish to call attention to a peculiar blood-containing cyst of large size which, though its precise nature is not yet clear, seems to match more closely with unicameral bone cyst than with any other type of cyst. Possibly some of the cases described as instances of aneurysmal giant cell tumor and benign bone aneurysm actually represent this lesion, of which we have studied 2 examples.

In 1 case—that of a boy of 17—the cyst involved the superior ramus of the pubis and caused such pronounced distention of this bone, especially inward and backward, that an expansion of the pelvic wall as big as a large orange could be felt through the rectum. In the roentgenograms the affected bone area presented a coarse soap bubble appearance (fig. 10). In the second case—that of a boy of 18—the cyst involved the second dorsal vertebra, having cystically transformed and expanded the body, the arch and the spinous process. The expanded body was luxated anteriorly, and, in addition, the cyst had caused pressure erosion of several neighboring ribs on the left side and of a part of the third

14. Platt, H.: Cysts of the Long Bones of the Hand and Foot, *Brit. J. Surg.* 18:20, 1930.

vertebra. In the roentgenogram, one could see that in this case, too, the altered body had a somewhat coarse soap bubble appearance. As was to be expected in view of the location and the size of this lesion, the patient already showed a number of abnormal neurologic manifestations on admission to the hospital; specifically, transverse myelitis developed after the cyst was explored.

In both cases, when exposing the lesion and opening into its thin wall, the surgeon was immediately confronted by a large hole containing much fluid blood, and the exudation of blood continued, though without spurting; the supply apparently came steadily from the inner wall of the

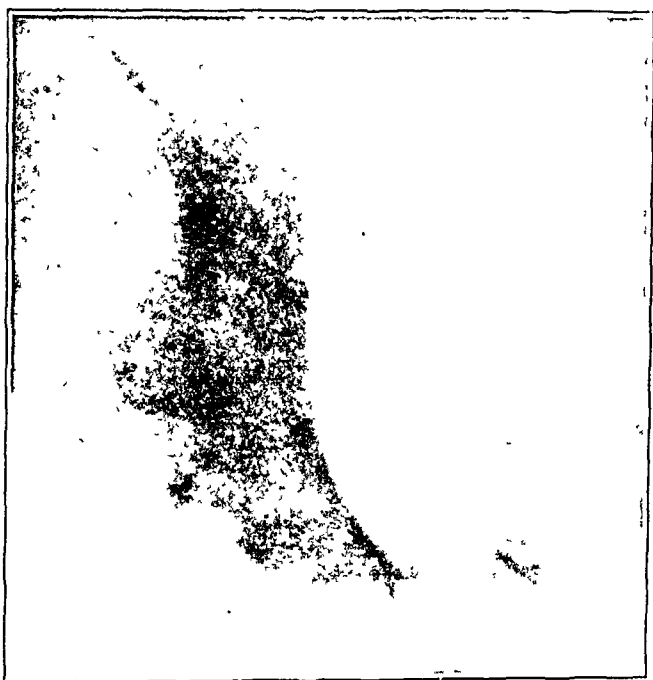


Fig. 10.—Roentgenogram of an aneurysmal cyst which has completely replaced a superior pubic ramus.

cyst. On microscopic examination, the wall's lining tissue, which in many places was not thick, was found elaborately vascular (fig. 11). Specifically, the connective tissue composing the lining wall was heavily permeated with delicate blood-filled capillaries and large distended or distorted venous channels. In some places, there was much free hemorrhage between the blood channels, and in these areas hemosiderin-bearing phagocytes and multinuclear giant cells were sometimes numerous. In fact, some of the larger venous spaces were even collared by collections of multinuclear giant cells. Further, between the vascular spaces and sometimes even around the larger ones, there were filamentous trabeculae

of connective tissue bone. The numerous and intercommunicating vascular channels were the source of bleeding into the cyst proper, and, indeed, when the cavity was entered, blood continued to flow copiously from it. However, in these cases, the absence of blood clot on the wall indicated that the blood in the cavity was not stagnant, and the blood-filled cavity could be regarded as being merely a large venous pool being steadily drained and freshly supplied.

The treatment of choice for such aneurysmal cysts is essentially like that for solitary unicameral bone cyst, namely, curettage of the wall and



Fig. 11.—Photomicrograph ($\times 20$) of part of the wall of the cyst shown in figure 10. Note the abundant vascular spaces, some of which are large and supported by filamentous trabeculae of connective tissue bone.

packing of the cavity with autogenic bone chips. The baneful consequences of intervention in the case in which the lesion was present in the dorsal vertebra were due solely to the peculiarly unfortunate location of the cyst.

SUMMARY

Solitary unicameral bone cyst is a lesion *sui generis*. It bears no relation whatever to giant cell tumor of bone, and in particular it does not represent a cystic-healing phase of this tumor. Nor is it to be linked

with enchondroma, fibroma or focus of fibrous dysplasia of bone which has undergone partial or extensive cystic degeneration. Further, it should not be regarded as representing the cystic expression of osteitis fibrosa, since to throw it into this wastebasket category (one which to us is also meaningless) is to obliterate its distinctiveness. Correspondingly, solitary unicameral bone cyst ought no longer to be classed as an expression of localized fibrocystic disease of bone or localized fibrous osteodystrophy—likewise blanket designations dating from a more primitive era of bone pathology.

Practically always, the lesion begins its development in the shaft, at or near an epiphysial cartilage plate, of some one of a few predilected long tubular bones. Indeed, in any representative series of cases, about half of the lesions will be found in the upper humeral shaft, and this region, together with the upper femoral shaft, will account for fully two thirds of all cases. The cyst is usually already large and well developed when attention is first drawn to its presence—usually by an infraction of the attenuated cortex. Anatomically, the lesion presents itself as a unicameral cavity filled with fluid and delimited by a thinned and often distended shaft cortex. The inner surface of this cortex, roughened and sometimes distinctly ridged, is lined by a rather thin connective tissue membrane yielding, as a rule, but little material to curettement. On microscopic examination, this material is found to consist mainly of fibrin clots containing some red blood cells and undergoing organization and even calcification and ossification. In an occasional case it also contains some cholesterol crystals, with or without nests of multinuclear giant cells and lipoid and hemosiderin-containing phagocytes.

As to pathogenesis, we favor the view, already proposed by Mikulicz,¹² that the lesion has its basis in a local disorder of development and bone growth, rather than, as proposed by Pommer,¹⁰ in a local intramedullary hemorrhage resulting in the development of an encapsulated pressure cyst from the continuous transudation of fluid into the area. We have tried to show also that the natural life cycle of the cyst has two stages. The first stage—that of active growth—persists as long as the cyst remains abutting on the epiphysial cartilage plate. The stage is usually interrupted when an area of *substantia spongiosa* becomes reconstructed between the plate and the cyst, in the course of healing of a spontaneous fracture. The cyst is then in the second stage—the latent or static—in which, while tending not to increase in size, it moves farther away from the plate as the longitudinal growth of the bone progresses.

Whether in the growing or in the static stage, solitary unicameral bone cysts are amenable to operative cure by curettage and filling with autogenous bone chips. Indeed, if the cyst is in a latent stage, it is almost

sure to show prompt obliteration in response to this treatment. If the cyst is still in its growing stage, it is often likewise quickly obliterated. However, particularly large cysts in this stage, or cysts which have been irradiated before being operated on, may fail to fill in completely and promptly, sometimes requiring a second intervention. Finally, it appears that spontaneous (nonsurgical) healing of solitary unicameral bone cyst occurs much less frequently than is commonly supposed. Radiation therapy by itself never leads to healing of the type of cyst in question and seems even to be contraindicated as an adjuvant to surgical intervention.

Attention has also been drawn to the rarity of solitary unicameral cyst in other than long tubular bones and to a peculiar type of blood-containing cyst which was described under the heading of aneurysmal cyst.

RECURRENT DISLOCATION OF THE PATELLA

A STUDY OF END RESULTS IN TWENTY-SEVEN CASES

S. SVERRE HOUKOM, M.D.

Formerly Anne C. Kane Fellow, New York Orthopaedic
Dispensary and Hospital

DULUTH, MINN.

The treatment of recurrent dislocation of the patella has been a fertile field for the growth and development of surgical ingenuity. As many as sixty different operative procedures have been devised for its correction. This study of 27 dislocating patellas treated at the New York Orthopaedic Dispensary and Hospital confirms my belief that one or two types of procedure, either separate or combined, are sufficient to give a stable symptomless knee. This is true for all types of cases. It is important also to emphasize relatively early operative treatment, since with this condition osteoarthritis is prone to occur sooner than in a normal knee.

CLINICAL FINDINGS

The group of cases here presented comprises 10 in which the condition was bilateral and 7 in which it was unilateral, or a total of 27 dislocating patellas which were treated by operation at the New York Orthopaedic Dispensary and Hospital in a thirteen year period between 1925 and 1938.

History.—Sex: All of the patients were female. This predominance among the female sex was found also among 27 patients seen in the dispensary but not admitted to the hospital for treatment. Only 3 of these clinical patients were male.

Age of Onset: The chronic recurrent type of dislocation has its onset chiefly in late childhood or early adolescence. The age of onset varied from $3\frac{1}{2}$ to 16 years, the average age of onset in 14 cases being 9.9 years.

Trauma: None of the patients gave a history of violent or severe trauma. Six gave no history of trauma at all. In 7 patients, the initial dislocation occurred when the patient was engaged in fairly strenuous activity, such as running, jumping or bending over. The recurrent attacks usually occurred also when running, jumping or doing acrobatic dancing. In 1 patient, the patella dislocated on ordinary walking. In 2 patients, the patella slipped when the knee was flexed. Three patients

From the New York Orthopaedic Dispensary and Hospital.

reported that their knees merely gave way and they fell and that because of this, they were unable to play games.

Joint Reaction: A severe joint reaction did not usually occur after this type of dislocation. A few patients did not have any pain. Most patients had moderate pain and swelling lasting a few days. Several patients had only momentary pain which disappeared as soon as the knee was moved and manipulated and the patella slipped back into place.

Frequency of Attacks: The frequency of dislocation varied greatly, occurring only once or twice a year in some patients; in others, as often as a dozen times a month. Although severe joint reactions are uncommon, the frequency of attacks in some cases must certainly cause chronic irritation in the joint, leading to osteoarthritis.

Physical Examination.—General Findings: On physical examination, most of these patients did not show any noteworthy findings besides the local knee condition. One patient had mild residual poliomyelitis, but the muscles of the involved knee were not appreciably affected, all muscle weakness being below the knee. Another patient had considerable shortening on the affected side ($3\frac{1}{2}$ inches [8.9 cm.]) due to growth disturbances in the epiphysial plates of the femur resulting from fracture in infancy. General ligamentous relaxation was noted in 4 cases.

Valgus Deformity of the Knee: Nineteen knees had valgus deformity varying from slight to 20 degrees. In 10 of these, the valgus was not more than 5 degrees. In the remaining 9 cases, the valgus varied from 5 to 20 degrees. One third of the entire group of 27 cases, therefore, had an appreciable degree of knock knee, which may have been a predisposing cause of dislocation.

Patellas: Three patellas were reported as being underdeveloped. Three had tight fascial bands on the lateral side. In 13 knees, the patella was said to be abnormally movable. It is difficult to say at what point a patella has abnormal mobility. With the knee in full extension, the normal patella has a considerable free range of motion both medially and laterally when the quadriceps muscle is relaxed. I have seen patients preoperatively in whom the amount of passive mobility of the dislocating patella did not seem greater than on the unaffected side.

Lateral Femoral Condyle: In only 1 case was the lateral femoral condyle stated to be underdeveloped in the preoperative examination. The only way that aplasia of this structure can be definitely determined is by exposure of the lateral condyle at the time of operation.

Quadriceps Muscle: Abnormalities of the quadriceps muscle were infrequent. In 1 case there were considerable atrophy and poor power. In 1 case in which the condition was bilateral, active extension of the knees was limited to 160 degrees, presumably owing to poor quadriceps power.

Knee Motion: All knees had full passive motion except in 1 case in which there was bilateral knee flexion deformity of 5 degrees. In 1 case in which the condition was bilateral there was marked ligamentous relaxation of the knee, and in 3 others, slight relaxation.

Gait: The gait was not abnormal unless an associated deformity, such as a short leg, was present.

Roentgen Findings.—In the roentgen examination of these patients, the usual anteroposterior and lateral views of the knee were taken. In addition, an anteroposterior view with the knee in acute flexion also was taken. This gives a good view of the patella resting in the intercondylar groove and its relation to the condyles of the femur.

The roentgenograms reproduced in this article show that marked structural abnormalities are uncommon. Some of the features which should be noted are:

1. Genu valgum of varying degree, which is easily seen, may be present.

2. The patella may be higher and more laterally placed than normal (fig. 1 *A*).

3. Lateral roentgenograms may show that the patella has slipped off with the knee in extension. This is the more common occurrence (fig. 2 *A*).

4. Occasionally, lateral roentgenograms show that the patella has slipped off with the knee in flexion (fig. 3 *B* and *C*, right knee).

5. In cases of the congenital type, the patella is dislocated laterally both in flexion and in extension (fig. 4 *A* and *B*).

6. The lateral condyle may be underdeveloped. Aplasia of this structure is difficult to determine by roentgen examination. Figure 4 *A*, which shows the anteroposterior view of the knee in flexion in a case of the congenital type, might be interpreted as showing underdevelopment of the lateral condyle. However, this view shows the more distal portion of the condyle, and at this level the lateral condyle has normally less elevation than the medial condyle.

Classification of Dislocating Patellas.—Cole and Williamson¹ divided their cases of dislocation of the patella into three different groups as follows: (1) acute traumatic dislocation, which may be an occasional cause of chronic recurrent dislocation; (2) congenital dislocation, in which the patella has developed away from its normal position and has never been where it belongs—the patella is found on the lateral side, resting firmly against the lateral femoral condyle; (3) chronic recurrent dislocation, usually due to certain underlying predisposing causes, the

1. Cole, W. H., and Williamson, G. A.: Chronic Recurrent Dislocation of the Patella, J. A. M. A. **102**:357-360 (Feb. 3) 1934.

majority of which occur without any acute trauma. In addition to these types, 2 of the cases in the group on which this study is based are classified under a separate heading because of severe knock knee deformity due to growth disturbances. One other case is classified separately because of poliomyelitis involving the extremity.

Using these criteria, the 27 dislocating patellas in this group were classified as follows: adolescent, 20; congenital, 4; due to severe knock

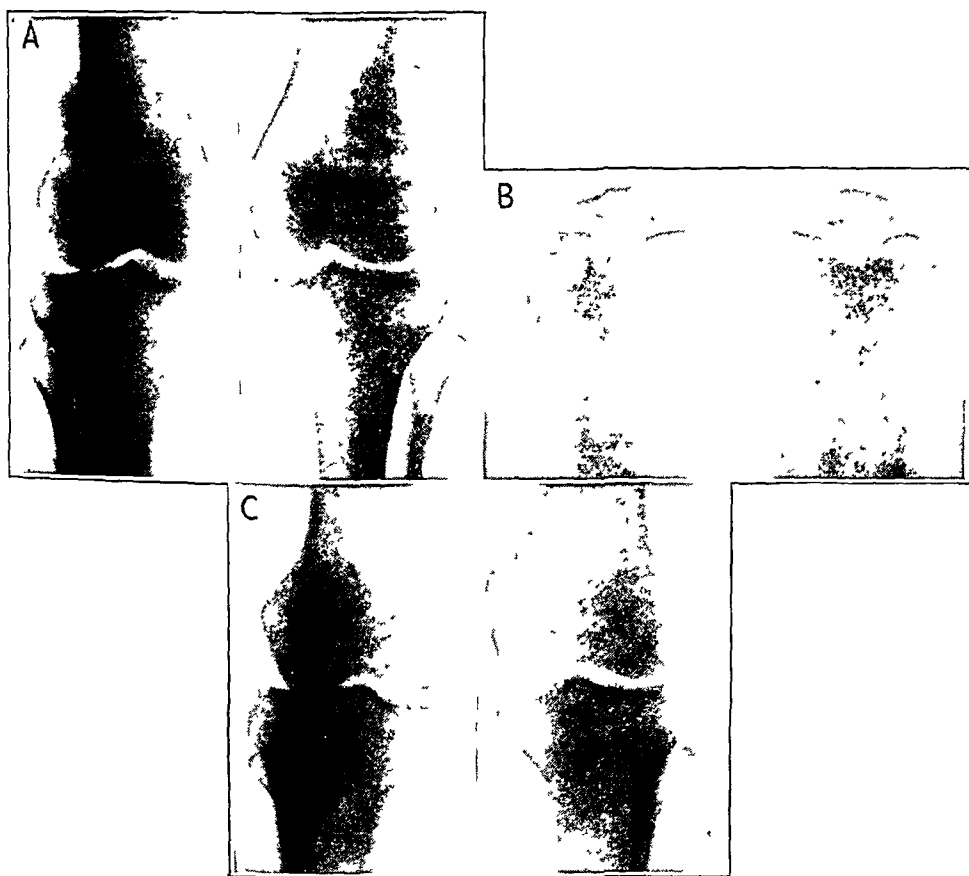


Fig. 1.—Roentgenograms of a patient with bilateral dislocating patella. In this case the patellas dislocated with the knees in extension. *A*, anteroposterior view before operation with the knees in full extension. The patellas are riding higher on the femur than usual. *B*, anteroposterior view before operation of the knees in acute flexion. In this position the patellas are in normal relation to the femoral condyles. *C*, after bilateral tibial tubercle transplant operation. The patellas are now resting in the proximal portion of the trochlear fossa in a more medial and distal position than before operation.

knee caused by (*a*) fracture in infancy and (*b*) chondrodysplasia, 2; due to residual poliomyelitis, 1; traumatic, 0.

The physical and roentgen examinations of these patients showed no marked deviation from normal in the majority of cases, and therefore

their condition belonged to the recurrent type of dislocation occurring in adolescence. Possibly in 2 of these cases, the dislocating patellas were of the congenital type, because both roentgen and operative findings showed marked lateral displacement with the patella firmly fixed in this position. Also, in 1 of the cases in which the condition was congenital, the patella began dislocating at $3\frac{1}{2}$ years of age, and this was the earliest onset in this group. None were of the severe traumatic type.

CAUSATION AND MECHANISM OF DISLOCATION

One of the more interesting features of recurrent dislocation of the patella is that the causation or the actual mechanism of the dislocation

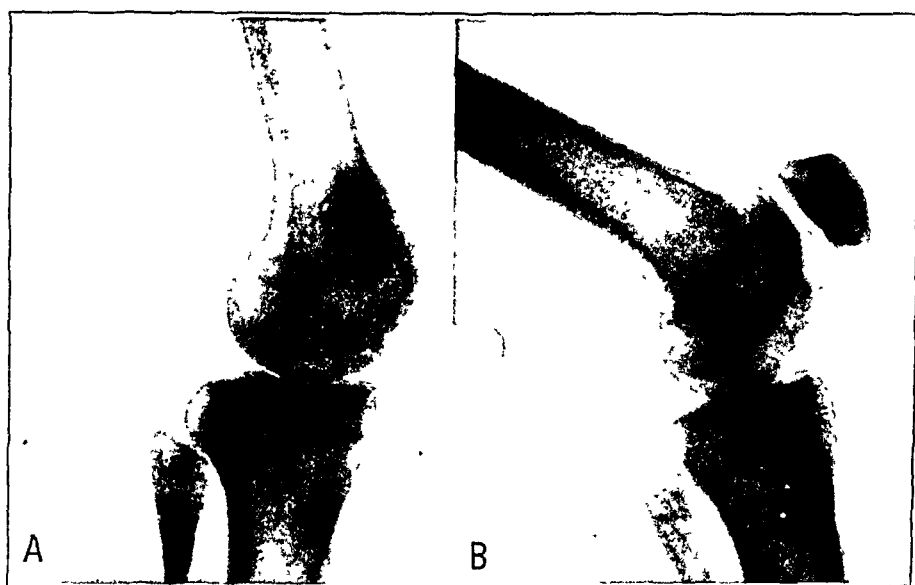


Fig. 2.—Lateral view roentgenograms of a knee: *A*, in extension, showing the patella laterally dislocated; *B*, in flexion, showing the patella in its normal relations to the femoral condyles.

remains obscure. As Gallie and LeMesurier² pointed out, in the majority of cases of the adolescent type, there has been nothing in the knee, except perhaps laxity of ligaments, to suggest the cause of the dislocation.

Some of the anatomic features of the normal knee joint are hereinafter reviewed because of their bearing on the mechanism of dislocation.³

2. Gallie, W. E., and LeMesurier, A. B.: *Habitual Dislocation of the Patella*, *J. Bone & Joint Surg.* 6:575-582 (July) 1924.

3. Frazer, J.: *Anatomy of the Human Skeleton*, ed. 2, London, J. & A. Churchill, 1920. Gray, H.: *Anatomy of the Human Body*, revised and edited by W. H. Lewis, ed. 23, Philadelphia, Lea & Febiger, 1936. Morris, H.: *Morris' Human Anatomy*, edited by C. M. Jackson, ed. 8, Philadelphia, P. Blakiston's Son & Company, 1925. Piersol, G. A.: *Human Anatomy*, ed. 9, revised, Philadelphia, J. B. Lippincott Company, 1936.

1. The deep fascia of the thigh as it descends to the knee blends with the fibrous expansion of the extensor tendon. The fascia is much thinner on the medial side of the patella than on the lateral side and blends much less with the tendon of the vastus medialis muscle than the lateral part of the fascia does with the vastus lateralis muscle. In full extension, only the lower third of the patellar articular surface rests on that of the condyles and its upper two thirds lies on the pad of fat which covers the lower and anterior part of the femur. In extreme flexion, only the upper third of the patella is in contact with the femur, and the lower two thirds rests on the fat pad between it and the tibia.

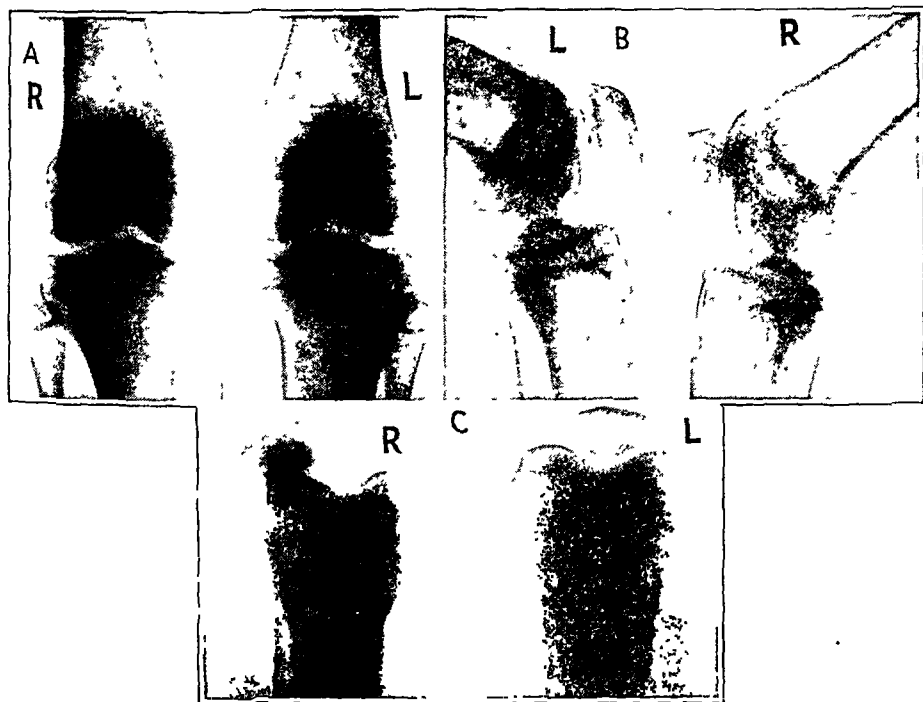


Fig. 3.—Roentgenograms of the knees of a patient with a dislocating right patella and a normal nondislocating left patella: *A*, anteroposterior view of the knees in extension, showing the right patella in its normal position; *B*, lateral view of the knees after the right patella dislocated on flexion; *C*, view showing the right patella slipping off the lateral condyle with the knees in acute flexion. The right and left knees are designated by *R* and *L*, respectively.

2. The patella is held in place as a result of the tension of the quadriceps muscle retaining it in its groove and partly owing to the attachments of the aponeuroses that lie beside it.

3. The vastus lateralis muscle is the largest part of the quadriceps femoris.

4. The greater strength of the vastus lateralis muscle is more than sufficient to overcome the resistance offered by the relatively more exten-

sive insertion of the vastus medialis muscle into the inner margin of the patella.

Thus it may be concluded that in the normal knee the fascia on the medial side of the patella is more easily torn, that the most stable position of the patella is midway between full extension and full flexion and that the components of the quadriceps muscle tending to pull the patella laterally are of greater strength and are acting at better mechanical advantage than those tending to pull the patella medially.

In cases of chronic dislocation of the patella, probably a variety of predisposing causes acting together are responsible for the dislocation. Important predisposing causes, several of which have been mentioned in the literature, are as follows:

Age.—Most of the cases occur at an age when strenuous activities are common. Also, at this age, joint structures have not lost the laxity present during the growing period.

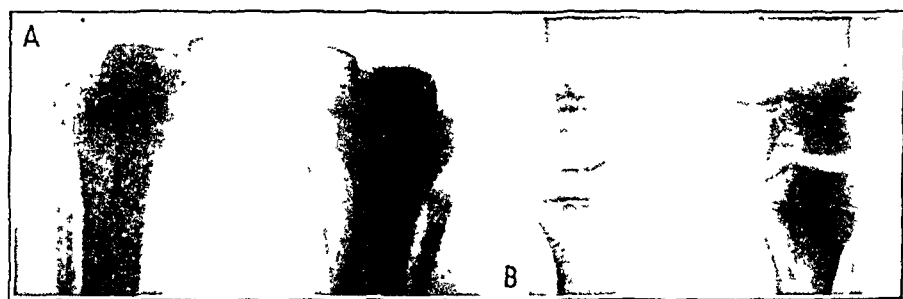


Fig. 4.—Anteroposterior views of bilateral congenital dislocating patella: *A*, in flexion; *B*, in extension. The patellas are permanently dislocated both in flexion and in extension.

Sex.—Normally there is an axial deviation of about 10 degrees between the femur and the tibia. This axial deviation tends to be greater in females because of the wider pelvis; the outward pull of the quadriceps muscle on the patella therefore would be greater than in males. As Winslow^{3a} brought out, this outward pull of the quadriceps muscle is probably a factor in causing dislocation. Normally, the quadriceps pulls in the long axis of the femur. The tibia and the femur are at an angle, and the resulting pull is therefore outward as well as upward.

Abnormal Anatomic Factors.—(*a*) Knee Valgus: Knee valgus varies greatly but must be of considerable importance in cases in which the valgus deformity approaches 10 to 15 degrees.

(*b*) Elongated Patellar Tendon: An elongated patellar tendon causes the patella to ride high on the femur.

3a. Winslow, N.: Complete Outward Dislocation of the Patella, *Ann. Surg.* 79:415-417 (March) 1924.

(c) **Tight Fascial Bands:** Tight fascial bands on the lateral side of the patella, holding the patella constantly in a more lateral position than normal, have been particularly emphasized as a factor by Ober.⁴ It may possibly be of more importance in the congenital type of dislocation in which the patella has developed in a lateral position.

(d) **Relaxed Medial Capsule:** Hauser⁵ felt that the trauma sometimes associated with these cases results in the tearing of the medial capsule and the fascia, this allowing the patellar tendon to be displaced laterally. The severity of trauma in many of the cases on which this study is based did not seem sufficient to cause much tearing of the medial capsule or aponeurosis.

(e) **Aplasia of the Lateral Femoral Condyle:** Aplasia of the lateral femoral condyle has frequently been mentioned in the literature as a predisposing cause of dislocation. As already stated, it is difficult to determine the presence of aplasia by physical and roentgen examination. Horwitz⁶ found this condition in only 3 of his 20 cases. The importance of this factor has probably been overemphasized.

It was noted in 8 knees that the patella dislocated when the knee was extended from the flexed position. This usually occurred when the knee had reached 165 to 175 degrees of extension. In some knees the patella was in the normal position in full extension, but active contraction of the quadriceps muscle caused the patella to subluxate laterally. Some patellas subluxated laterally when the knee was merely passively extended. As Ober brought out, dislocation of the patella in extension is probably due to the fact that at 165 to 175 degrees extension, the patella begins to lose the support of the lateral condyle, especially if the patellar tendon is elongated. In passing the condyle with the quadriceps pulling at an angle, it is fairly easy for the patella to slip off the lateral side. In other cases it seemed because of knee valgus and abnormal direction of the quadriceps pull, that, as the knee was extended, the patella was pulled up on the lateral condyle or its lateral aspect, instead of into the patellar groove. On further extension, the patella slipped off the lateral condyle. The fact that these patellas slip off laterally in extension during examination does not necessarily explain the disability that patients of this type have. It seems possible that when they are doing something fairly strenuous, such as running or jumping, the patella slips off laterally during extension, and with sudden flexion occurring, the patella is unable

4. Ober, F. R.: *Slipping Patella or Recurrent Dislocation of the Patella*, J. Bone & Joint Surg. **17**:774-779 (July) 1935.

5. Hauser, E. D. W.: *Total Tendon Transplant for Slipping Patella: A New Operation for Recurrent Dislocation of the Patella*, Surg., Gynec. & Obst. **66**:199-214 (Feb.) 1938.

6. Horwitz, M. T.: *Recurrent or Habitual Dislocation of the Patella: Critical Analysis of Twenty Cases*, J. Bone & Joint Surg. **19**:1027-1036 (Oct.) 1937.

to get back onto the trochlear fossa and stays dislocated during flexion also, thus causing considerable disability.

In 4 knees examined, the patellas dislocated laterally at 90 to 110 degrees of flexion. Dislocation in flexion is more common in cases of the congenital type or in those in which a severe degree of valgus exists. There seem to be three possible ways in which the patella is dislocated on flexion of the knee. The patella may slip off laterally during extension and remain in the same position during flexion. Laxity of the medial capsule and aponeurosis favor this. The dislocation may be of the congenital type in which the patella is fixed in the lateral position. When the patella approaches 90 to 100 degrees of flexion, it comes to a more lateral position, its upper portion resting almost wholly against the lateral condyle. In this position a fair degree of outward rotation of the tibia is possible. With considerable valgus present, the outward force acting on the patella tends to make it slip laterally.

Although it has been stated that in most of these cases examination does not usually show any marked deviation from normal, if the clinical, roentgen and operative findings are carefully studied in individual cases, abnormalities are often found. These abnormalities are slight in some cases, it is true, but it apparently does not take much to upset the normal mechanism which stabilizes the patella.

TREATMENT

In this group, the age at operation varied from 4 to 22 years. Most of the operations were done between 12 and 20 years of age. Thirteen patients waited anywhere from six months to eleven years before operation was done. The average period between onset of dislocation and operation was four and three-tenths years.

The operation most commonly performed in treating these patients at the New York Orthopaedic Dispensary and Hospital is transplanting the tibial tubercle with the attached patellar tendon. This operation is similar to the one recently described by Hauser. It has been used at the New York Orthopaedic Dispensary and Hospital since 1932. This procedure was done on 23 knees. In this operation, the tibial tubercle with the attached ligamentum patellae is removed as a block of bone and transplanted into a slot made on the medial side of the tibia, usually 1 or 2 cm. medially, and 1 to 2 cm. distally from its normal insertion. Chromic catgut sutures through the periosteum and the fascia are used to hold the transplanted tubercle in place. If there are tight fascial bands on the lateral side of the patella, they are severed. In some cases the medial capsule is plicated if it is thought to be relaxed.

This operation accomplishes two things:

1. By bringing the patella to a more distal position, the patella gets effective support from the lateral condyle when the knee is in extension.

2. The direction of pull of the quadriceps muscle on the patella is changed so that the component of force tending to pull the patella laterally is eliminated.

In knees in which considerable knock knee is present, the outward pulling force may not be eliminated entirely by the transplant operation and supracondylar osteotomy also will be necessary. This was done in 9 knees.

There was no constancy in the findings reported at operation. An underdeveloped lateral femoral condyle was noted in 4 cases. Usually, this structure is not exposed sufficiently during the transplant operation to determine whether aplasia is present. In 5 cases, tight fascial bands or tight aponeuroses on the lateral side of the patella were reported. However, in 12 cases, it was thought advisable to divide the lateral structures, although whether they were a deforming factor in all of them is not mentioned. In 3 cases, the quadriceps muscle was not in line with the patellar tendon and was therefore exerting an abnormal lateral pull on the patella. This is also more common than noted because a fair degree of knee valgus was present in one third of the cases. In 1 bilateral case, the patellas were found completely dislocated on the side of the lateral femoral condyles. They were held there by tight fascial bands and seemed to have developed in this position.

The synovial membrane of the knee joint was inspected in 2 cases, and it was found thick and congested, with villous hypertrophy. This is a significant finding since in many of these knees osteoarthritis will eventually develop unless the chronic irritating factor of dislocating patellas is corrected by operation.

Postoperative Treatment.—After operation, a long leg cast is applied and kept on for six weeks. At the end of this time, the cast is removed, and a roentgenogram is made to see whether the transplanted block of bone has firmly united in its bed. All of these patients showed firm union in six weeks. Massage and gentle motion are given, and in another week or two the patient is allowed up with crutches, and gradual weight bearing is started. Motion and normal gait return rapidly, and for most patients normal activities are possible at three months.

END RESULTS

End results are classified as excellent, good and poor. A patient with an excellent end result has no patellar slipping, no recurrence of dislocation, no symptoms and no restriction of activity. Anatomically, the patella is in normal position on flexion and extension. Roentgenograms show the absence of arthritic changes, with the patella in a more distal position and riding in the patellar groove.

A good result is one in which the patella does not dislocate, but there may be slight tipping on flexion or extension without symptoms. Roent-

genograms may show slight arthritic lipping without clinical evidence of arthritis, and there may be slight lateral displacement of the patella.

A poor result is one in which the patella dislocates at the time the cast is removed and motion started or which does not dislocate for several months after the operation but subsequently does so.

There were 22 knees with a follow-up period of one to seven years on which the tibial tubercle transplant operation was done. The average follow-up period for this group was three and five-tenths years. Eleven, or 50 per cent, of the knees showed an excellent result; 9, or 40 per cent, showed a good result, and 2 knees, or 10 per cent, showed a poor result. This makes 90 per cent satisfactory results of this type of operation.

One of the poor results was that of a patient who had a growth deficiency at the lower femoral epiphysis. She was still in the growth period, and knee valgus occurred to the same extent as before the supracondylar osteotomy. The other patient with a poor result had slight lateral subluxation of the patella on extension with coarse crepitation on motion. It was thought best to do a retransplant operation on this patient. In spite of the second operation, the patella still subluxated, and at the time of writing, this patient has been readmitted for another operation.

The fascial and capsular structures on the lateral side of the patella were cut in 12 knees at the same time as the tibial tubercle was transplanted. Six of these showed excellent results; 4, good results; 1, poor, and 1 had the retransplant already mentioned.

The medial capsule was reefed or plicated in 8 knees at the time of the transplant operation. In 1, the result was excellent, in 6, good and in 1, poor.

Both plication of the medial capsule and the release of the lateral structures were done in 6 knees. In 1, the result was excellent, in 4, good and in 1, poor.

Nine supracondylar osteotomies were done in patients who had tibial tubercle transplants. The amount of genu valgum varied between 10 and 20 degrees, most of the knees having 15 degrees of valgus. Five of these patients had supracondylar osteotomies before the transplant, and the osteotomy was not enough to cure the dislocation. Of the 5, 2 were immediately cured by the transplant. One had a second osteotomy soon after the transplant because valgus had partially recurred and because it was found at operation that the patella was not stable in flexion even after the tibial tubercle has been transplanted. One (in whom the condition was due to a growth disturbance) had a transplant operation which failed to stabilize the patella. A second osteotomy was done, but valgus recurred, and the patella still dislocated.

One patient, in whom the condition was bilateral, had supracondylar osteotomies just before the transplant operation; thus the value of the

osteotomies in this case is not known. One other patient, whose condition also was bilateral, had osteotomies one year after transplants, not because of dislocation but because it was thought that osteotomies would give a more mechanically sound joint.

Of the 9 cases in which supracondylar osteotomies and transplants were done, in 2, the results were excellent, in 5, good and in 2, poor. On the other hand, there were 10 knees which had transplants alone without osteotomy; all of these showed excellent results. None of those which had transplants alone had an appreciable amount of valgus. In knees with severe knock knee deformity of 15 to 20 degrees, it is important to correct the valgus by supracondylar osteotomy before doing the transplant operation. In 3 patients, supracondylar osteotomy failed to stabilize the patella because of the recurrence of knock knee. Subsequent tibial tubercle transplants were not adequate to prevent dislocation until a revision of the osteotomy was done and the knock knee corrected. In the average patient with recurrent dislocation of the patella, with only moderate genu valgum (5 to 10 degrees), the transplant operation can be done alone with the expectation that no further operation will be necessary.

In 1 case in which the condition was bilateral, supracondylar osteotomy alone was done. Both knees showed a good result years later. There was 10 degrees valgus deformity before operation.

Plication of the medial capsule alone was done in 2 knees. Six years later, 1 knee showed a good functional result, the patella subluxating slightly to 160 degrees extension. In the other case, a transplant of the tibial tubercle was required one and one-half years later because of the recurrence of dislocation.

CONCLUSIONS

The causation of chronic recurrent dislocation of the patella in adolescence is obscure but probably involves a combination of factors acting together on a certain age group, made up chiefly of the female sex.

In many instances, chronic recurrent dislocation of the patella is not much disabling but nevertheless should be treated by operation to prevent the early onset of osteoarthritis.

Operative treatment by means of the tibial tubercle transplant operation is not technically difficult and is satisfactory. This should be combined with plication of the medial capsule and release of tight fascial bands laterally, when necessary.

In the more severe types of deformity, with considerable genu valgum, both supracondylar osteotomy and tibial tubercle transplant will have to be done. The complete correction of valgus deformity should be emphasized.

TUMORS OF TENDON SHEATHS

HERMAN CHARACHE, M.D.

BROOKLYN

Tumors of tendon sheaths, excluding ganglion, are rare. Buxton,¹ whose work on tendon sheath tumors is so frequently quoted, stated:

. . . This structure [tendon sheath] is a specialized part of connective tissue and is therefore subject to the same neoplasms as other connective tissue. Such neoplasms are not uncommon. Therefore one searches for some reason why tendon sheaths should be so immune from tumor formation, and it is very difficult to find any facts bearing on this point.

According to Canavero,² only 1 or 2 cases are found in every 2,000 hospital or clinic admissions. At the Brooklyn Cancer Institute, the Cumberland Hospital and the Jewish Sanitarium and Hospital for Chronic Diseases, among 10,500 hospital admissions and 157,000 clinic admissions in the past ten years, only 5 cases of tumors of the tendon sheaths were found. And yet these 5 cases all occurred in the year 1939-1940. Are these tumors becoming more prevalent than before? One can only tell if more cases are reported in the literature.

Because of the rarity of these tumors and the lack of information on the subject in modern textbooks, a complete review of the literature was made, and the following classification of tumors of tendon sheaths was evolved:

Benign

1. Ganglion
2. Xanthomatous giant cell tumor
3. Lipoma
4. Hemangioma
5. Lymphangioma
6. Fibroma
7. Osteochondroma

Malignant

1. Synovioma
2. Spindle cell sarcoma
3. Chondrosarcoma

BENIGN TUMORS OF TENDON SHEATHS

Ganglion.—Ganglion is a benign cystic neoplasm containing mucinous or gelatinous material which is the product of collagenic degener-

1. Buxton, S. J.: Brit. J. Surg. **10**:469, 1923.

2. Canavero, M.: Policlinico (sez. chir.) **41**:341, 1934.

ation. It arises from the connective tissue of the joint capsule or the tendon sheath. This view was first brought out by Clarke³ in 1908, was accepted by many writers and was included in Dean Lewis'⁴ report of 40 cases of ganglion in 1934. Occasionally, ganglion may arise from the joint capsule and invade the tendon sheath by contiguity, without communicating with either cavity.

The tumor is most prevalent during adolescence and early adult life. Some cases have been reported in children (Lewis). Trauma is considered a predisposing cause in the formation of ganglion. In 50 cases reported by De Orsay, Mecray and Ferguson,⁵ 19 (38 per cent) were associated with trauma. The dorsum of the wrist is the most frequent site of formation. Other sites, in order of frequency, are: the volar surface of the wrist and the fingers, the dorsum of the foot and the popliteal region. The outstanding symptom is the presence of a tumor. While pain is not a dominant symptom, the patient may complain of weakness and pain on grasping or lifting. Most ganglions removed in the operating room confirm the clinical diagnosis because the diagnosis of any other tumor is seldom made. Almost all tumors in the wrist are diagnosed as ganglion.

The treatment of choice is complete surgical excision of the ganglion, including the deep ramifications between and around the adjoining tendon sheaths and joint ligaments, preferably in the operating room. Only a small percentage lend themselves to safe removal at the clinic dressing table.

Considering the various tumors found in tendon sheaths, one can only mention the method of striking the tumor with a heavy object in order to condemn it. Surely one would not recommend this treatment for a tumor of unknown type in another part of the body. True, ganglion is the most commonly found tumor in this region, but tumors of other types also may be found, as will be discussed in this paper. The surgical axiom, "See what you do, and do what you see," applies to any part of the human body and extends to the treatment of tumors of the tendon sheaths.

The treatment of ganglion by the injection of sclerosing solutions has been tried with some success in isolated instances.

Sixty cases of ganglion were recorded at the Cumberland Hospital from 1931 to 1941. In 54 cases (90 per cent), the patients were female; in 6, they were males. The oldest patient was a 68 year old man; the youngest was a 7 year old girl. Two cases occurred in the first decade of life; 19, in the second; 22, in the third; 8, in the fourth; 7, in the fifth, and 2, in the seventh. Forty-six (77 per cent) occurred on the

3. Clarke, W. C.: *Surg., Gynec. & Obst.* 7:56, 1908.

4. Lewis, D.: *Surg., Gynec. & Obst.* 59:344, 1934.

5. De Orsay, R. H.; Mecray, P. M., Jr., and Ferguson, L. K.: *Am. J. Surg.* 36:313, 1937.

dorsal surface of the wrist, and 5 (8, per cent) on the volar surface. Six (10 per cent) occurred in the region of the foot; 2 (3 per cent), in the popliteal region, and 1 (1 per cent), in the finger. The size varied from that of a pea to that of a walnut. The duration of the disease varied from four months to ten years, with an average of twenty-one months. Trauma as a predisposing cause was found in 8 cases (13 per cent); in 5 of these the trauma was at the site of healed fractures. The right and the left extremities were equally involved. In 2 cases, the condition was bilateral (wrist). Only 10 patients (17 per cent) complained of pain.

Xanthomatous Giant Cell Tumor.—A soft tissue tumor of the tendon sheath, varying in size from that of a pea to that of a hen's egg, yellowish brown, lobulated, surrounded by a capsule and composed of polyhedral or spindle cells, dense connective tissue, giant cells, large vesicular lipoid cells, pigment of hemosiderin and, occasionally, cholesterol crystals, fibrocartilage or even bone trabeculae—this type of tumor is often referred to as giant cell sarcoma, endothelioma, myeloma, xanthoma and granuloma. Little wonder then that the average reader on this subject is so confused as to the identity of this type of tumor. Geschickter and Copeland,⁶ and Lewis, who made a thorough study of the literature on this subject and studied 52 cases of their own in the laboratories of Johns Hopkins Hospital, Baltimore, restricted the name "giant cell tumor" or "xanthomatous giant cell tumor" to this type of growth of the tendon sheath.

Next to ganglion, the giant cell tumor is the most common growth found in the tendon sheath. In more than 50 per cent of the cases, it is located in the tendon sheaths of the fingers at the metacarpophalangeal or interphalangeal joint near the tendinous insertion or next to a sesamoid bone. Next in frequency are the palm, the wrist, the toes, the ankle, the arms and the legs. In 32 of the 50 cases reported by Lewis, the growth was located in the tendon sheaths of the fingers. In the remainder, it was elsewhere in the hand or about the foot and the ankle. Based on a careful histologic study, Geschickter and Copeland and Lewis all agreed that there is a definite relation between this tumor and the sesamoid bones.

Diagnosis is difficult since the symptoms and signs are not characteristic of this tumor alone. Roentgen examination may reveal some fibrocartilage and bone trabeculae in certain cases only. Xanthelasma of the skin in other parts of the body and hypercholesteremia may be found in some cases.⁷ The treatment is complete excision. The prog-

6. Geschickter, C. F., and Copeland, M. M.: Tumors of Bone, New York, American Journal of Cancer, 1936, p. 736.

7. Ollerenshaw, R.: Brit. J. Surg. 10:466, 1922.

nosis is good; recurrence is rare. The tumor, according to Ewing⁸ and many others, does not metastasize. However, Ragins⁹ found 6 cases in the literature in which bone was invaded. Three additional cases were reported by Geschickter and Lewis.¹⁰

Lipoma of Tendon Sheaths.—Lipoma of the tendon sheaths is rare. In 1924, White¹¹ emphasized the "extreme rarity of this condition, as evidenced by the small number of cases reported and by the fact that no surgeon has reported more than one case of his own observation." In 1922, Strauss¹² found only 18 cases reported in the literature and added a case of his own. His study and complete analysis of these cases contributed a great deal toward the study of this subject. In 1931, Straus¹³ found 34 cases reported and added 1 of his own. Two cases were reported by Geschickter and Lewis¹⁰ in 1934. One case was reported by each of the following authors: Valdoni (1931),¹⁴ Canavero (1934),² Periset (1938)¹⁵ and Jadevaia (1940).¹⁶ These represent a total of 41 cases. I wish to add 2 additional cases, making a total of 43 cases.

Lipoma of the tendon sheaths occurs in two forms: the simple lipoma, which often occurs symmetrically in both hands and usually involves a single tendon sheath, and the arborescent type, which is analagous to the fat of the appendices epiploicae and which because of its arborescence involves more than one tendon sheath. The latter is the more prevalent. Histologically, the arborescent type contains more fibrous tissue and is more vascular but is otherwise indistinguishable from any other lipoma.

The extensor tendons of the hands and the feet are most commonly involved. The former are twice as frequently involved as the latter. The symptoms vary with the size of the tumor; the larger the tumor, the greater the pressure symptoms along the neighboring nerves and the greater the interference with the movements of the tendons. Tingling, numbness and stiffness of the fingers are often complained of. The majority of the patients are male and between the ages of 15 and 30.

Diagnosis is difficult; in only 3 cases has the diagnosis been made before operation. The tumor is soft, sometimes giving a strong suggestion of fluctuation. It may become firmer in consistency when it is chilled with an ice bag. This has been employed as a diagnostic aid in

8. Ewing, J.: *Neoplastic Diseases*, ed. 4, Philadelphia, W. B. Saunders Company, 1940, p. 282.

9. Ragins, A. B.: *Ann. Surg.* **93**:683, 1931.

10. Geschickter, C. F., and Lewis, D.: *Am. J. Cancer* **22**:96, 1934.

11. White, J. R.: *Surg., Gynec. & Obst.* **38**:489, 1924.

12. Strauss, A.: *Surg., Gynec. & Obst.* **35**:161, 1922.

13. Straus, F. H.: *Ann. Surg.* **94**:269, 1931.

14. Valdoni, P.: *Chir. d. org. di movimento* **15**:509, 1931.

15. Periset, P.: *Chir. d. org. di movimento* **24**:78, 1938.

16. Jadevaia, F.: *Gior. di med. mil.* **88**:137, 1940.

a number of cases. Some roentgenologists are able to differentiate lipoma from other soft tissue shadows.

Treatment is complete surgical removal. In most cases part of the tendon sheath has to be removed with the tumor.

The prognosis is good. Recurrence seldom takes place when the tumor is completely removed. The arborescent type is more likely to recur, because one or more of its ramifications may be left behind.

Hemangioma of the Tendon Sheath.—Hemangiomas in general are relatively common tumors; however, hemangioma of the tendon sheaths is rare. Burman and Milgram¹⁷ found but 10 cases reported in the literature up to 1930 and added 6 of their own. In 1937, Harkins¹⁸ found 24 cases, including 1 of his own. Another case was reported by Piccagli¹⁹ in 1939. To this number I wish to add an additional case, making a total of 26 up to the time of writing.

Although hemangiomatous tumors are considered by Ewing and others to be of congenital origin, in only 3 of the reported cases of hemangioma of the tendon sheath was the growth known to have been present at birth. In more than half the cases there has been a history of trauma previous to noticing the tumor. However, although trauma of the extremities is so common, hemangioma develops in few cases. Trauma is much more frequent in male than in female patients, yet hemangioma of the tendon sheaths is twice as prevalent in female as in male patients. The condition usually occurs during early adult life. The upper extremity is involved twice as frequently as the lower. The sites in the upper and the lower extremities in the order of frequency are as follows: the forearm, the wrist, the leg, the hand, the foot and the thigh.

Pain and the presence of a tumor are the only symptoms which bring the patient to the hospital. Pain is usually due to angiolithic concretions or nerve pressure. The median or the radial nerve is usually involved; less frequently, the ulnar nerve. The pain is aggravated during complicated movements of the fingers, such as piano playing, and with the increase in size of the tumor. Occasionally there will be no symptoms at all except the presence of the tumor, and the patient will wait many years before coming for treatment. The longest period between the appearance of the tumor and reporting for treatment was seventeen years; the average was four years.

The tumor varies in size and shape. It may be the size of a hazelnut or the size of an orange. It may be spheroid or spindle shape. It decreases in size when the extremity is elevated or when it is compressed with the fingers. It increases in size in the dependent position

17. Burman, M. S., and Milgram, J. E.: Surg., Gynec. & Obst. **50**:397, 1930.

18. Harkins, N.: Hemangioma of Tendon or Tendon Sheath, Arch. Surg. **34**: 12 (Jan.) 1937.

19. Piccagli, G.: Chir. d. org. di movimento **24**:533, 1939.

or on circular compression of the limb. The overlying skin is freely movable and takes a deeper purplish hue during the dependent position or circular compression. The tumor moves with the movement of the involved tendon. Occasionally one can palpate the angiolithic concretions within the tumor. The tumor itself has a cystic feel. The concretions show up well on roentgen examination.

Complete surgical excision is the treatment of choice, and no other treatment can be substituted for it. The prognosis of angioma of tendon sheaths is good. The rarity of recurrence, of functional disturbance or of malignant transformation bespeaks its results.

Lymphangioma.—Only 5 cases of lymphangioma of the tendon sheath were found in the literature by Harkins in 1937. There has been no other case reported up to the time of writing. The clinical course differs little from that of hemangioma.

Fibroma.—There have been 51 cases of fibroma of the tendon and the tendon sheaths reported in the literature up to the time of writing. Janik²⁰ found 19 cases reported in the literature before 1927. Torchiana²¹ and dal Pozzo²² each reported a case in 1931. Thirty cases were reported from Johns Hopkins Hospital by Geschickter and Copeland⁶ in 1934. In the series of Geschickter and Copeland, the majority of the patients were between 10 and 25 years of age. The next most common age group was between 35 and 45. The greater part of the lesions were in the upper extremity.

Fibroma of the tendon sheaths is a small circumscribed firm nodule, not adherent to the skin but intimately attached to the tendon sheath, simulating subcutaneous fibroma in any other part of the body. In some instances, it is associated with multiple neurofibromatosis, as observed by Brunschwig.²³ It does not recur after complete excision. Because of its circumscribed nature, it lends itself to complete excision more readily than any other tumors in this region. Part of the tendon sheath has to be excised with the tumor.

Osteochondroma.—Osteochondroma of the tendon sheath usually arises near the osseous insertion of the tendon, where precartilaginous tissue normally exists. Histologically, it does not differ from similar lesions in other parts of the body and is subject to malignant transformation. It varies in size from that of a cherry to that of a hen's egg, and interferes with the movements of the tendons, resulting in pain. The majority of cases have occurred during adult life. The hands and the feet are most commonly involved. The treatment is complete excision. Part of the tendon sheath and, in some instances,

20. Janik, A.: *Ann. Surg.* **85**:897, 1927.

21. Torchiana, L.: *Arch. ital. di chir.* **28**:436, 1931.

22. dal Pozzo, C.: *Cancro* **2**:116, 1931.

23. Brunschwig, A.: *Tumors of the Hands and Feet*, St. Louis, C. V. Mosby Company, 1939, p. 109.

even part of the tendon may have to be sacrificed. Twenty-two cases have been reported in the literature up to the time of writing; Geschickter and Copeland²⁴ found 15 cases reported and added 7 additional cases.

MALIGNANT TUMORS OF TENDON SHEATHS

Synovioma.—Synovial tumors are rare; still rarer are synovial tumors of the tendon sheath. In 1937, Coley and Pierson²⁵ found only 20 cases of synovial tumors reported in the literature. They reported 15 additional cases from the Memorial Hospital for the Treatment of Cancer and Allied Diseases, New York, from 1900 to 1937, only 1 of which was of possible tendon sheath origin. A year later, Berger²⁶ reported 5 additional cases and analyzed the cases already reported. He concluded as follows: "Our own cases included, there are actually 23 cases in all presenting specific synovial factors, of which 11 are articular, 9 in bursae, and 3 in tendon sheaths." The 15 cases of Coley and Pierson were not included in this report. In the same year, Jönsson²⁷ reported 14 cases of synovial tumors from Radiumhemmet in Stockholm, Sweden, 6 of which occurred in tendon sheaths. One case of synovioma was reported by Hutchison and Kling²⁸ in 1940, and 16 cases were reported by DeSanto, Tennant and Rosahn in 1941²⁹; 2 of these were of tendon sheath origin. This makes a total of 69 cases of synovial tumors, of which 12 (17 per cent) originated in tendon sheaths.

Jönsson divided synovial tumors into synovialoma and synovial fibrosarcoma. The former has a greater tendency to pulmonary metastasis, involves the regional lymph glands and is radiosensitive. The latter has a relatively more benign course, almost never involves the regional lymph glands, does not tend to pulmonary metastasis so commonly and is radioresistant.

Histologically, synovialoma is composed of spindle cells, polygonal and endothelial cells and small or large cystic cavities lined with cuboid or endothelial cells. Occasionally, epithelial cells group themselves to enclose a lumen, simulating a gland structure, the so-called pseudo-alveoli.

Synovial fibrosarcoma is less cellular and is composed of a greater amount of fibrous tissue and spindle cells, the nuclei of which are larger and narrower than in synovialoma.

24. Geschickter and Copeland,⁶ p. 733.

25. Coley, B. L., and Pierson, J. C.: *Surgery* **1**:113, 1937.

26. Berger, L.: *Am. J. Cancer* **34**:501, 1938.

27. Jönsson, G.: *Acta radiol.*, 1938, supp. 36, p. 1.

28. Hutchison, C., and Kling, D. H.: *Am. J. Cancer* **40**:78, 1940.

29. DeSanto, D. A.; Tennant, R., and Rosahn, P. D.: *Surg., Gynec. & Obst.* **72**:951, 1941.

Grossly, synovial tumors are of soft consistency, even fluctuating at times, although some are reported as firm. They vary in size from that of a walnut to that of an orange. In the larger tumors, the overlying skin may be infiltrated and even ulcerated. The superficial veins are markedly dilated. The cut surface is grayish white or brownish, showing cystlike cavities containing brownish or yellowish fluid. In describing the gross appearance of the tumors, Jönsson stated: "It is striking how the operator received more the impression of a chronic inflammatory process than a tumor."

The clinical course of synovioma is the same, whether it occurs in the joint capsule, the tendon sheath or the bursae. The diagnosis is most difficult. The pathologist is usually the one who makes the diagnosis after removal of the tumor, and this he does after a great deal of deliberation and study. Subjective symptoms are few. The patient first notices a swelling. Pain, weakness and a tingling sensation of the fingers or the toes are later manifestations. The tumor itself is not characteristic of synovioma alone, even under the most scrupulous clinical study. Roentgen examination is of no avail in helping the diagnosis; however, it may rule out other types of tumor. The wrist, the hand, the ankle and the foot are the most common sites of the tumor. Male and female patients are equally affected, and the tumor is most prevalent between the ages of 20 and 50.

Early high amputation is the treatment of choice. Berger quoted Sabrazes as follows:

. . . It is amputation which should impress itself from the first examination. The family, the physician, the surgeon, the pathologist hesitate proposing such a sacrifice in the presence of a tumor which seems to be so slightly malignant in the first stage of its development. Later one is forced to this intervention; one undertakes it, alas, too late.

Coley and Pierson stated that any operable tumor which by its location suggests the probability or even the possibility of synovioma should be removed by wide excision followed by roentgen therapy after the diagnosis is confirmed by the pathologist. In the event of recurrence, they recommended prompt amputation, provided the lungs are free from metastasis. Although they agreed that the tumor is not radio-sensitive, they recommended radiation therapy for postoperative and nonoperative treatment.

The prognosis of synovioma, as given by Coley and Pierson, is 20 per cent five year cures and 40 per cent three year survivals.

Spindle Cell Sarcoma.—Spindle cell sarcoma is the rarest of all tendon sheath tumors. Geschickter and Copeland³⁰ could find but 5 cases at the laboratories of Johns Hopkins Hospital. In all of them the patients were children or young adults. In 2, the tendon of the

30. Geschickter and Copeland,⁶ p. 738.

quadriceps femoris muscle was involved; in 1, achilles tendon; in 1, the region anterior to the ankle joint, and in the fifth, the region above the phalanx of the toe. In all of them there was recurrence after primary excision. Cooperman³¹ reported a case of spindle cell sarcoma of the right foot in a woman of 22 involving the tendon sheath of flexor brevis digitorum. An additional case is reported hereinafter from the Brooklyn Cancer Institute in which the growth involved the region of the achilles tendon.

Chondrosarcoma.—An equally rare tumor of the tendon sheath is chondrosarcoma. Two cases were reported by Geschickter and Cope-land.²⁴ They cited 1 case of Jones³² and another of Kienböck.³³ A fifth case was reported by Buxton and a sixth by Janik. In 2 of the cases, the growth occurred at the achilles tendon.

REPORT OF CASES

Benign Tumors of Tendon Sheaths

CASE 1 (Lipoma).—A. S., a white woman 40 years of age, was admitted to the Cumberland Hospital on April 14, 1940, complaining of a swelling over the left wrist. About two years previous to admission, she had fallen in a bathtub and injured the left forearm. A week later she noticed the swelling. For the next two years, she could not use her hand effectively without experiencing a certain amount of pain, particularly over the radial side of the hand. The hand would "fall asleep" at frequent intervals, especially the thumb and the index finger. In the last two weeks the tumor greatly increased in size, and the pain was aggravated, radiating from the radial side of the hand to the elbow. The past history and the familial history were otherwise uneventful.

Physical examination revealed a well developed white woman, not acutely or chronically ill. The temperature, pulse and respiration rates were normal; the blood pressure was 190 systolic and 110 diastolic. An irregular firm cystic mass was found over the dorsal surface of the lower third of the forearm and measured 6 by 2 cm. The tumor appeared to be deeply situated and fixed to the underlying structures. The overlying skin was of normal appearance and freely movable. There was no limitation of movements of the fingers, but the patient experienced pain over the tumor in the forearm when she opened or closed her hand. The rest of the physical examination did not reveal any pathologic condition. The blood count was within normal limits; the urine was normal, and the Wassermann test of the blood was negative.

The patient was scheduled for removal of the tumor under local anesthesia. An incision was made over the mass. A tumor presented itself, pushing the muscle in front of it. On careful dull dissection, a spindle-shaped encapsulated fatty tumor, 7 by 2 cm., was found underneath the muscle fibers. The tumor was firmly attached to the sheath of the extensor digitorum communis muscles. The tumor was removed, and the wound was closed in the usual manner.

The pathologic report was lipoma. The patient made an uneventful recovery.

CASE 2 (Lipoma).—R. R., a boy aged 15, was admitted to the Brooklyn Cancer Institute on March 9, 1940, complaining of a swelling of the left hand.

31. Cooperman, M. B.: J. Bone & Joint Surg. **14**:173, 1932.

32. Jones, H. T.: J. Bone & Joint Surg. **6**:407, 1924.

33. Kienböck, A.: Röntgenpraxis **3**:406, 1931.

About seven years before, he had noticed a small painless lump on the dorsum of the left hand. The tumor grew progressively larger, reaching the size and shape of a pear.

Examination revealed a pear-shaped tumor over the dorsum of the wrist and the web between the thumb and the index finger, freely movable on extension and flexion of the hand. The tumor was soft and cystic and not attached to the

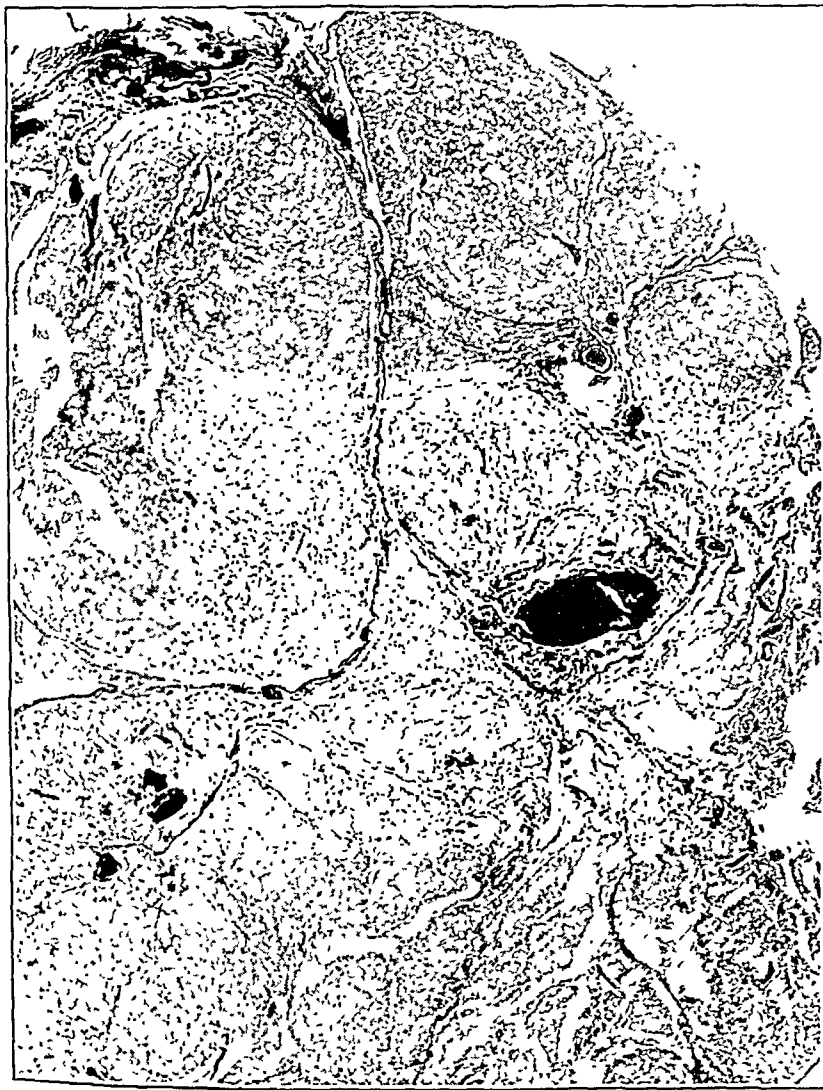


Fig. 1 (case 2).—Photomicrograph of arborescent lipoma of tendon sheath.

skin or underlying structures and measured 7.5 by 5 cm. The overlying skin was slightly reddened but not inflamed. Roentgen examination of the wrist did not reveal any pathologic condition of the bone or any opaque substance.

In the operating room under local anesthesia an elliptic incision was made over the tumor. A lobulated yellow elastic mass was found attached to the sheath of the tendons of the extensor pollicis longus and extensor digitorum communis muscles. It completely filled the space between the two tendons and

quadriceps femoris muscle was involved; in 1, achilles tendon; in 1, the region anterior to the ankle joint, and in the fifth, the region above the phalanx of the toe. In all of them there was recurrence after primary excision. Cooperman³¹ reported a case of spindle cell sarcoma of the right foot in a woman of 22 involving the tendon sheath of flexor brevis digitorum. An additional case is reported hereinafter from the Brooklyn Cancer Institute in which the growth involved the region of the achilles tendon.

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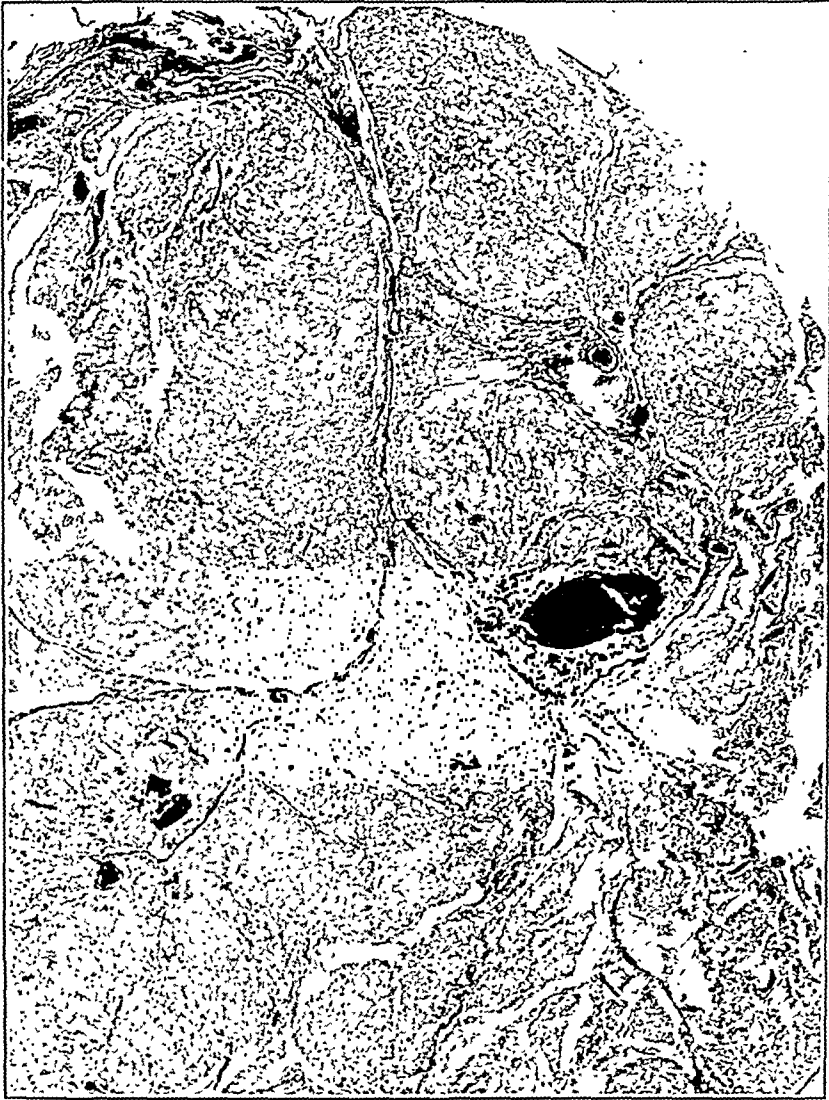


Fig. 1 (case 2).—Photomicrograph of arborescent lipoma of tendon sheath.

skin or underlying structures and measured 7.5 by 5 cm. The overlying skin was slightly reddened but not inflamed. Roentgen examination of the wrist did not reveal any pathologic condition of the bone or any opaque substance.

In the operating room under local anesthesia an elliptic incision was made over the tumor. A lobulated yellow elastic mass was found attached to the sheath of the tendons of the extensor pollicis longus and extensor digitorum communis muscles. It completely filled the space between the two tendons and

bulged to the surface. The tumor was removed without difficulty, and the wound was closed in the usual manner.

The pathologic report was lipoma (fig. 1).

CASE 3 (Hemangioma).—G. DeM., a 13 year old white boy, was admitted to Cumberland Hospital on March 4, 1939, complaining of a swelling of the left forearm. The swelling was first noticed at the age of 3. At that time it was



Fig. 2 (case 3).—Photomicrograph of hemangioma of tendon sheath.

the size of a cherry but it grew progressively larger. The swelling would "go up and down" the forearm as the hand was opened and closed. It did not interfere with the boy's activities and was painless.

Examination revealed a soft cystic ill defined mass on the ulnar surface of the lower third of the left forearm, which measured 3 cm. in diameter. When the forearm was held up, the tumor diminished in size. The tumor mass moved with the movements of the fingers.

In the operating room with the patient under local anesthesia an incision was made over the mass. A multilobulated purplish blue cystic tumor, measuring

about 2.5 by 3 cm., was found between the flexor pollicis longus muscle and the tendon of the brachioradialis muscle. When the tumor was removed by dull and sharp dissection from the tendon sheath of the brachioradialis muscle, to which it was intimately attached, part of the tendon sheath had to be removed with it. It contained several small dark red nodules (phleboliths). The pathologic report was cavernous angioma (fig. 2). The patient made an uneventful recovery.

CASE 4 (Fibroma).—O. T., a white woman aged 55, was admitted to the Jewish Sanitarium and Hospital for Chronic Diseases on Oct. 16, 1939, with a



Fig. 3 (case 4).—Fibroma of the tendon sheath: A, before operation; B, gross specimen removed at operation.

diagnosis of hypertensive cardiovalvular disease and right hemiplegia. On physical examination it was disclosed that the patient had a tumor of the right index finger. The patient stated that eighteen years before she had noticed a small tumor of the distal phalanx of the right index finger, which grew slowly toward the palm. It had grown more rapidly during the last three years and prevented her from grasping objects. She experienced also some pain from time to time. Examination revealed an irregular sausage-shaped tumor along the flexor tendon of the right index finger from the distal phalanx to the hypothenar eminence (fig. 3). The tumor was of a soft consistency, not attached to the skin, slightly

movable and moved with the extension and flexion of the index finger. Roentgen examination revealed no abnormalities. A provisional diagnosis of xanthomatous giant cell tumor was made.

Operation was performed with the patient under local anesthesia. The tumor involved the tendon sheath of the index finger, as previously outlined. It was



Fig. 4 (case 4).—Photomicrograph of fibroma of tendon sheath.

removed without difficulty, leaving the white glistening tendon bare of its sheath. The patient made an uneventful recovery. The pathologic report was fibroma (figs. 3B and 4).

Malignant Tumors of Tendon Sheaths

CASE 5 (Spindle Cell Sarcoma).—D. M., a white man aged 20, was admitted to the Brooklyn Cancer Institute on April 11, 1940, for radiation therapy

following excision of a tumor of the right heel in another hospital. Three years previous to admission to that hospital, he had noticed a small lump on the inner side of the right heel. It did not give him any trouble until shortly before admis-

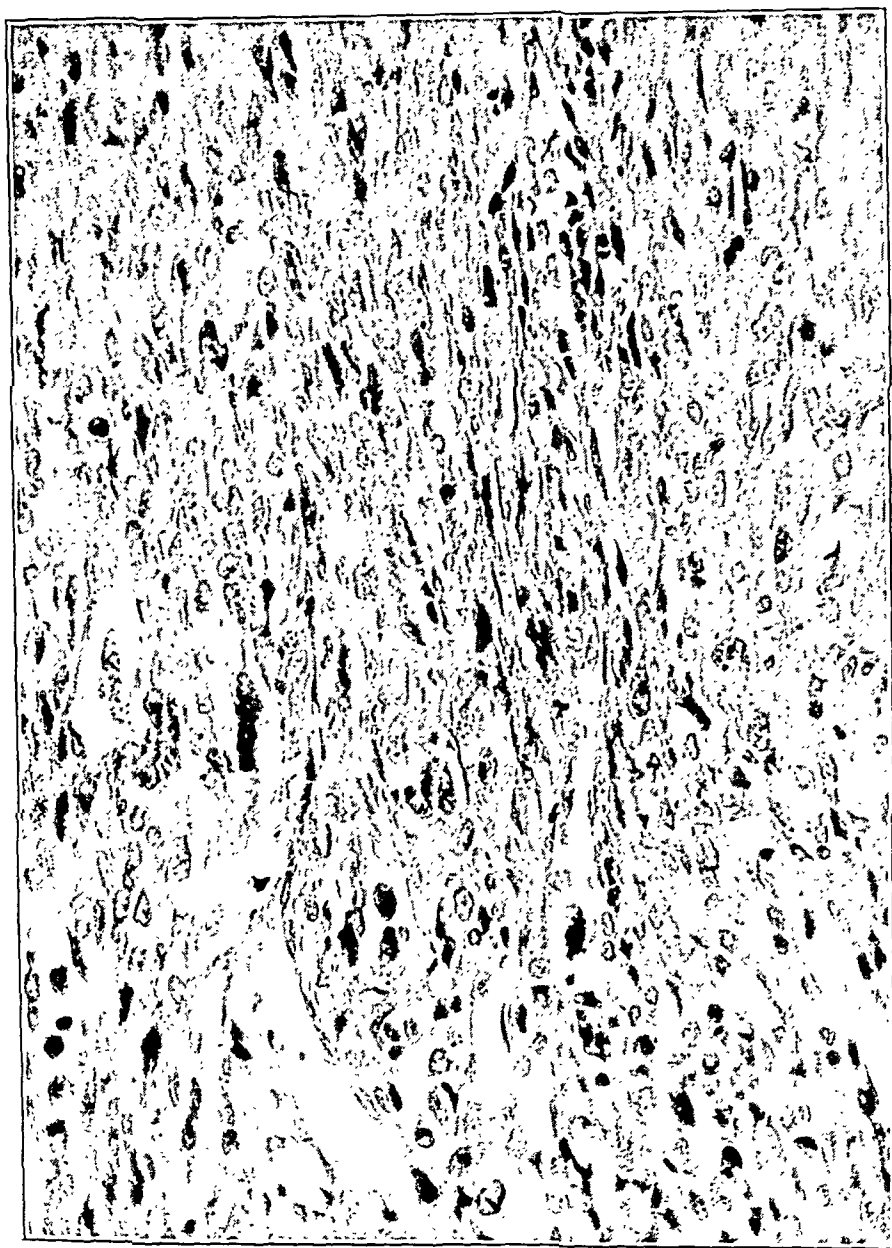


Fig. 5 (case 5).—Photomicrograph of spindle cell sarcoma.

sion, when he noticed that the swelling had increased in size and was associated with pain on walking. He was unable to wear a shoe on that foot because of the pain. On March 30, 1939, he was admitted to the hospital, where a tumor the size of an orange was found in the inner and posterior side of the right heel in the region of the achilles tendon. The tumor was firm and fixed to the under-

lying tissue. The center was friable and necrotic. The tumor was excised locally. The pathologic report, which was later confirmed by the department of pathology of the Brooklyn Cancer Institute, was spindle cell sarcoma (fig. 5).

On admission to the Brooklyn Cancer Institute, the patient was found to be a well developed young man, not acutely or chronically ill. A partially healed infected scar, measuring 6 by 8 cm., was found on the medial surface of the right heel. The surrounding area was indurated. The inguinal glands were not enlarged. Roentgen examination of the leg, the foot and the lungs showed no evidence of pathologic condition. The Wassermann test of the blood was negative; the blood count and blood chemistry were within normal limits. The urine was normal.

After roentgen therapy, the wound remained healed until February 1940, when it broke down. The ulcerated area was excised, and a full thickness graft was applied. The excised tissue contained malignant cells showing radiation changes. The wound healed, and the patient was free from any symptoms when he was discharged on July 17. He returned to the hospital on Jan. 20, 1941 complaining of pain in the chest and hemoptysis. At this time, roentgen examination of the chest revealed pulmonary metastasis and large pleural effusion. Examination of the aspirated fluid showed the presence of sarcomatous cells. The patient died on February 18. Consent for autopsy was not obtained.

SUMMARY

Tumors of tendon sheaths are rare.

A critical study and a classification are made of the cases reported in the literature.

Sixty-five new cases are reported, 60 of ganglion, 2 of lipoma, 1 of hemangioma, 1 of fibroma and 1 of spindle cell sarcoma.

END RESULTS OF A NEW INCISION FOR FELON (INFECTION OF THE ANTERIOR SPACE)

JEROME J. WEINER, M.D.

NEW YORK

On incising the anterior closed space, besides the external signs of swelling, redness and tenderness together with a point of entry and throbbing pain (which is worse at night), one finds edema and swelling of the perpendicular connective tissue fibers. Pus is interspersed between the fibers, and the tuft of the phalanx shows evidences of softening. In cases of advanced infection, the tuft and part of the shaft of the phalanx are destroyed, and in cases in which the infection has reached a late stage, the entire phalanx is necrotic. In the latter type of case, an attempt should be made to preserve the base of the phalanx since it possesses regenerative powers.

Early sections of the distal portion of the phalanx reveal polymorphonuclear exudation into the marrow. Roentgen examination at this stage does not reveal any evidences of the destruction of bone. This is natural, because osteomyelitis is seen in the roentgenogram only after there has been a sufficient accumulation of microscopic areas of inflammation and necrosis to produce a gross lesion.

Figure 2 is a photomicrograph of a section from the finger of a 13 year old boy which was punctured forty-eight hours prior to operation. It reveals fibrous tissue periosteum about the cortex of the bone, and in some areas the bony spicules reveal a diminution in osteocytes. The marrow shows fat cells surrounded by dense masses of polymorphonuclear cells and round cells.

Figure 3 is a photomicrograph of a section of the finger of a 20 year old male patient who gave a history of having injured his finger two weeks before operation. This section reveals the disappearance of the marrow fat cells in addition to the changes found in figure 2.

Figure 4 is a photomicrograph of a section of the finger of a 23 year old man whose injury occurred three weeks before operation. This section shows production of granulation tissue consisting of new capillaries, fibroblasts, lymphocytic infiltration and deposition of collagen. This is found within the bone marrow.

Figure 5 is a sagittal section of a normal thumb. It demonstrates clearly the density of the connective tissue trabeculae in the vicinity of the tuft.¹ Division of these fibers is essential, if one is desirous of obtaining adequate drainage of infection of the anterior space. If the connective tissue fibers are necrotic, their removal together with the tuft of the distal phalanx will prevent further invasion of the bone and thus shorten the healing period. Neither the median incision nor the lateral

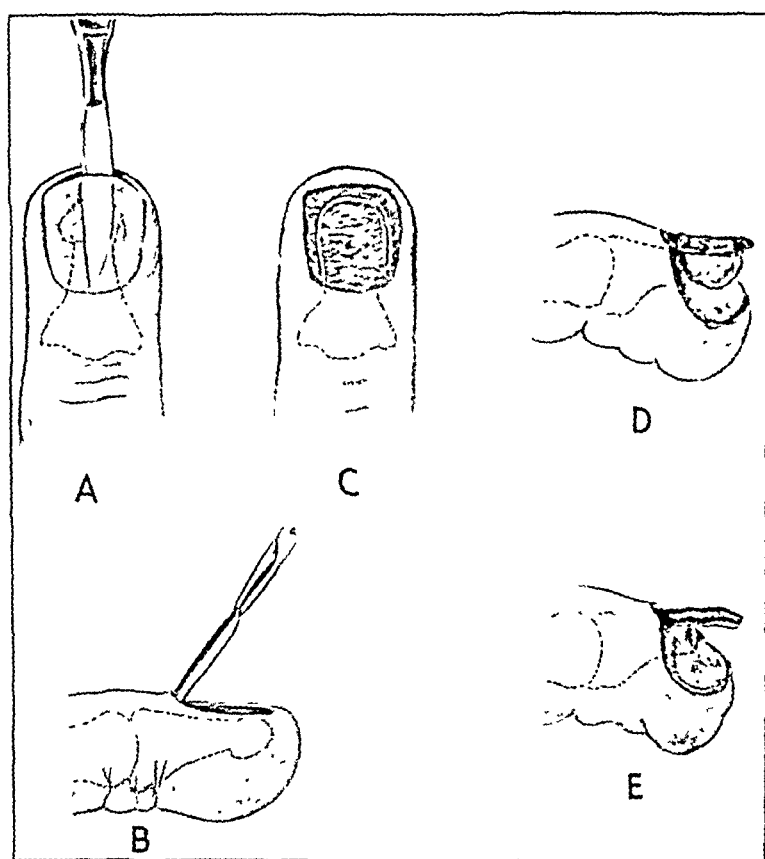


Fig. 1.—Diagram of the incision for infections of the anterior space showing: *A* and *B*, the method of detaching the nail from its bed, matrix and skin attachments; *C* and *D*, the inverted U-shaped incision carried down close to the tuft and to the distal portion of the terminal phalanx; *E*, the ample exposure obtained and the resultant gross lesion following removal of the tuft, if it is found to be involved.

hockey stick incisions divide the perpendicular fibers completely. The result is that these fibers form a thick plug of necrotic tissue which

1. Brickel, A. C. J.: *Surgical Treatment of Hand and Forearm Infections*, St. Louis, C. V. Mosby Company, 1939.

interferes with drainage and dams back the infection into the haversian canals and the bone cells. Roentgenograms taken a few weeks after incision invariably show evidences of bone destruction. It is only after the plug of necrotic tissue is removed and the diseased bone extrudes itself that healing takes place. This process requires a long period of treatment. The fish mouth incision completely divides the connective

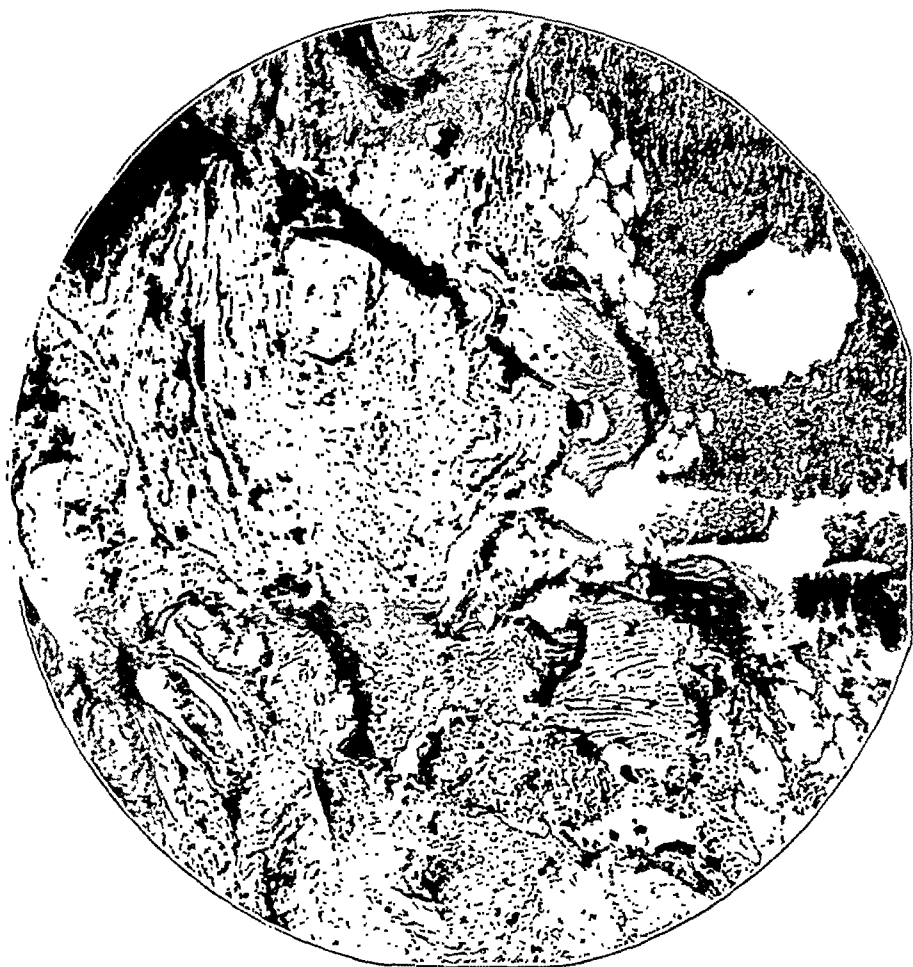


Fig. 2.—Photomicrograph showing fibrous tissue periosteum about the cortex of the bone. In some areas the bony spicules reveal a diminution in osteocytes. The marrow shows fat cells surrounded by dense masses of polymorphonuclear cells and round cells.

tissue trabeculae and gives adequate drainage. However, it leaves an ugly scar with an area of hyperesthesia above and an area of anesthesia below it.² Figure 6 shows the end results of fish mouth incisions.

2. Mason, M. L.: *Minnesota Med.* 20:485 (Aug.) 1937. Koch, S. L.: *Pennsylvania M. J.* 40:597 (May) 1937.

Figures 7 and 8 (cases 1 and 2) show instances in which the tuft was removed together with the necrotic connective tissue fibers.

Figures 9 and 10 (cases 3 and 4) are composed of roentgenograms taken in cases in which the tuft was left intact.



Fig. 3.—Photomicrograph showing the disappearance of the marrow fat cells in addition to the changes shown in figure 1.

The healing period in cases 1 and 2 was curtailed by three weeks as compared with that in cases 3 and 4.

Figure 11 (case 5) corroborates Kanavel's³ theory with regard to the cause of bone felon. His contention was that the distal phalanx has

3. Kanavel, A. B.: *Infections of the Hand*, Philadelphia, Lea & Febiger, 1939.



Fig. 4.—Photomicrograph of a section showing production of granulation tissue consisting of new capillaries, fibroblasts, lymphocytic infiltration and deposition of collagen. This is found within the bone marrow.

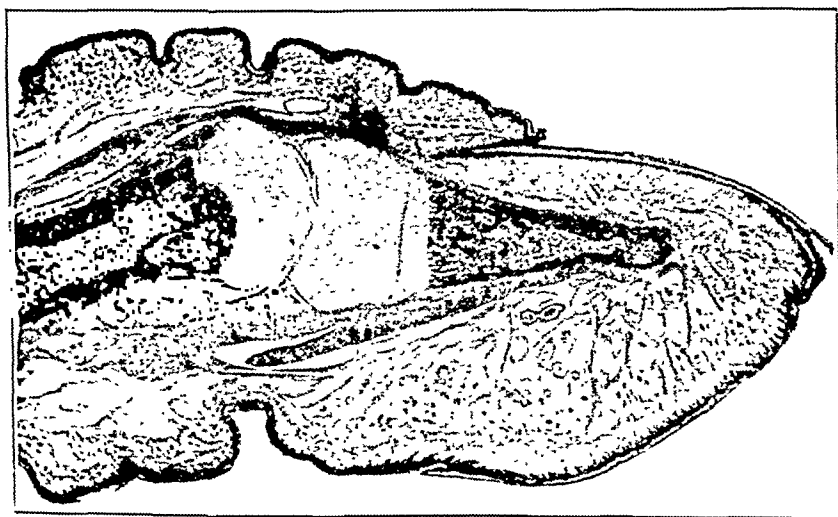


Fig. 5.—Sagittal section of a normal thumb showing the density of the connective tissue trabeculae in the vicinity of the tuft.



Figure 6
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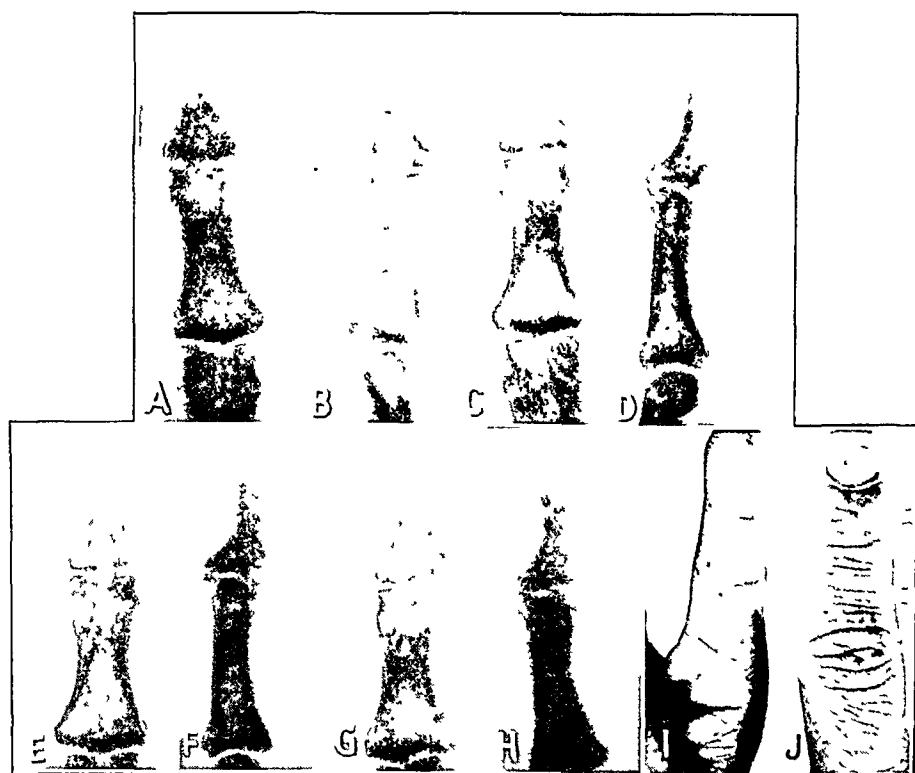


Figure 7
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a dual blood supply. He stated that owing to edema and pressure on the main blood supply to the diaphysis necrosis of the bone ensues, that the epiphysis lies outside of the closed space and receives a separate blood supply and that early in the disease it is not involved. Even though the major portion of the phalanx is destroyed, if the surgeon retains the base of the phalanx, regeneration invariably ensues. This applies to adults as well as to children. In case 5, a 25 year old white man showed evidence of complete destruction of the distal phalanx. At operation the major portion of the phalanx was removed, and the base was left intact. Within five weeks, the phalanx except for the tuft regenerated.

In case 6 (fig. 12), a white man 25 years of age gave a history of having punctured his right index finger on a piece of metal while he was at work. A few days later the finger swelled and pained him a great deal. The pain was throbbing and kept him awake at night. He went to his family doctor, who made an incision on the volar aspect of the finger extending beyond the distal interphalangeal crease and a lateral incision on the outer aspect of the digit which also crossed the interphalangeal crease. The finger did not drain adequately, and during the third week of his injury the patient presented himself at my office. The finger was swollen, and both incisions were closed by a thick plug of necrotic tissue. Roentgen examination of the index finger revealed evidences of destruction of the distal phalanx and part of the head of the middle phalanx. There were evidences of suppurative tenosynovitis involving the deep flexor tendon. With the patient under general anesthesia, the nail was avulsed, and a horseshoe incision was made around the tuft of the distal phalanx. A large amount of pus and necrotic connective tissue together with the major portion of the phalanx was

EXPLANATION OF FIGURE 6

Photographs showing the end results of fish mouth incisions in 2 cases.

EXPLANATION OF FIGURE 7

A and *B*, roentgenograms taken in case 1 two days after injury, showing no bone involvement; *C* and *D*, taken after operation at which the tuft of the bone was excised; *E* and *F*, taken one month after operation, showing evidence of regeneration of the phalanx; *G* and *H*, taken six weeks after operation, showing the phalanx completely regenerated. *I* and *J*, photographs showing end results. There is no scar on the volar aspect of the finger, and the new nail has completely regenerated.

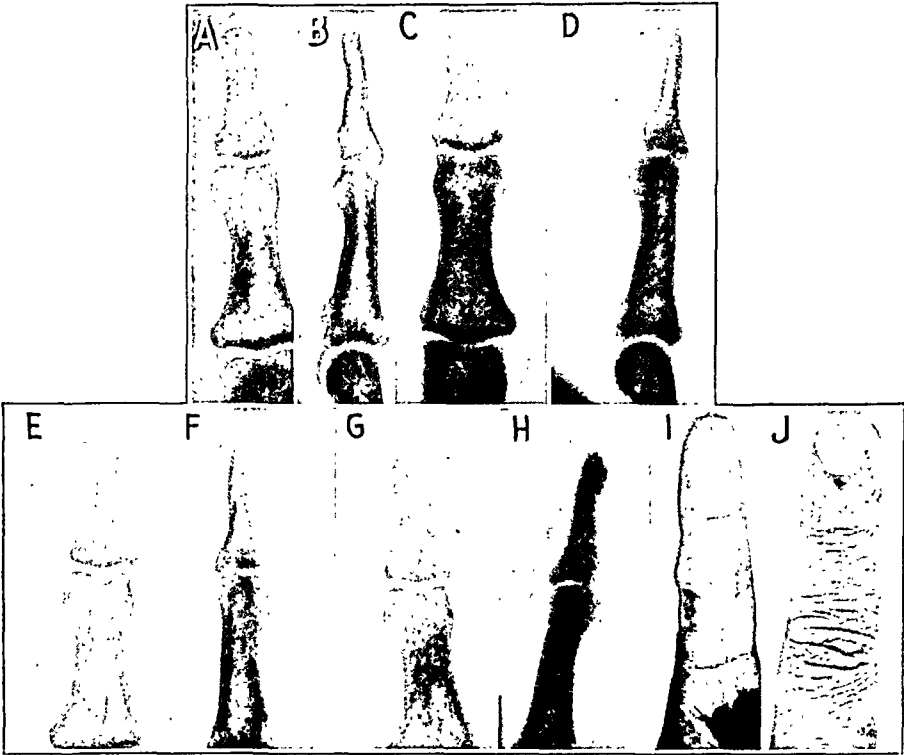


Figure 8
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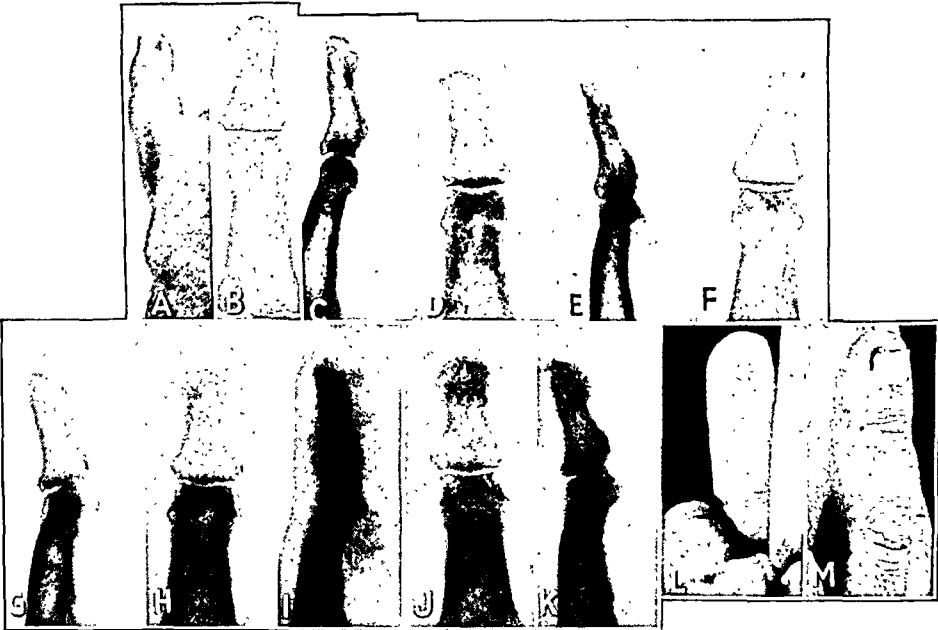


Figure 9
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removed. The wound was packed with iodoform gauze, and a wet dressing was applied. The series of roentgenograms taken during the course of treatment shows that part of the base of the distal phalanx had regenerated and that the flexor profundus tendon remained intact at its insertion into the base of the phalanx. Except for an extension defect in the finger, the functional result was good. The finger was held in a partially flexed position by the contracture of the scar on the volar aspect of the finger.

The end results in cases 1, 2, 3 and 5 showed that scarring on the volar aspect of the finger was absent and that the nail had regenerated. Sensation of the finger was not impaired.

SUMMARY AND CONCLUSIONS

Photomicrographs are presented which show invasion of the bone marrow by infection long before the roentgenogram or the naked eye could perceive evidence of bone destruction.

Comparative studies of cases are presented to show that whenever the tuft of the phalanx is removed early in a case of infection of the anterior space, the healing period is shortened. The tuft is removed only if the connective tissue fibers attached to the bone are edematous or necrotic.

EXPLANATION OF FIGURE 8

A and *B*, roentgenograms taken in case 2 three days after injury, showing no evidence of bone involvement; *C* and *D*, taken after operation at which the perpendicular fibers were found to be necrosed and were removed with the tuft of the bone; *E* and *F*, taken one month after operation, showing that there is no further invasion of bone cells and that regeneration is taking place; *G* and *H*, taken at the end of six weeks, showing the bone completely regenerated. *I* and *J*, photographs showing the end results. There is no scar on the volar aspect of the finger, and the new nail has completely regenerated.

EXPLANATION OF FIGURE 9

A, photograph taken in case 3 seven days after injury, showing the site of the infection. *B* and *C*, anterior and lateral roentgenograms, showing no bone involvement; *D* and *E*, anterior and lateral views taken fourteen days after incision, showing roughening of the phalanx; *F* and *G*, anterior and lateral views taken four weeks later, showing decalcification of the phalanx; *H* and *I*, anterior and lateral views taken eight weeks later, showing decalcification of the phalanx; *J* and *K*, anterior and lateral views taken three months later, showing normal bone; *L* and *M*, photographs showing end results. There is no scar on the volar aspect of the finger, and the new nail has regenerated.

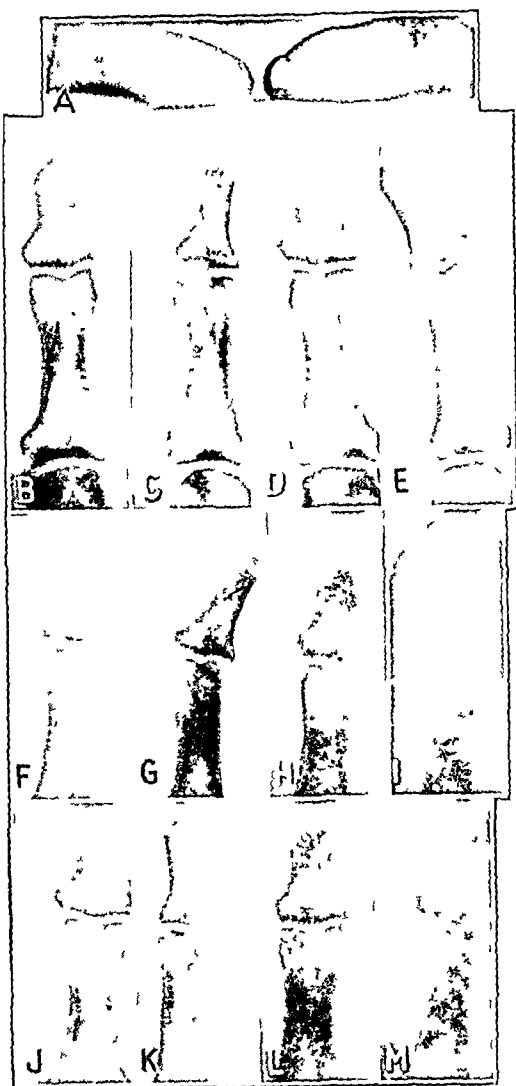


Figure 10

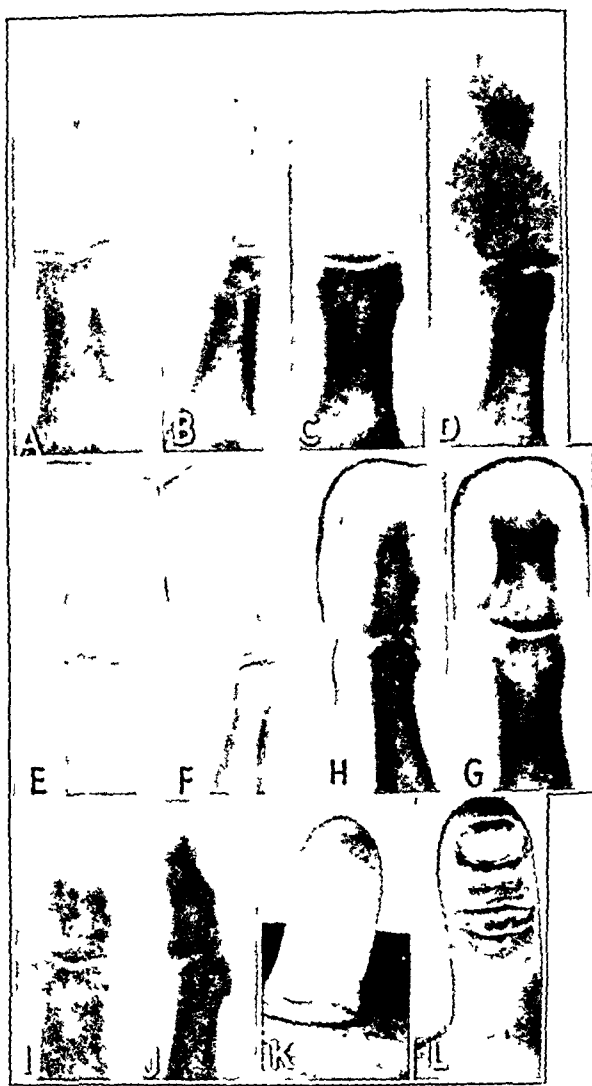


Figure 11

Fig. 10 (case 4).—*A*, comparative photograph showing the normal and the diseased thumb *B* and *C*, anteroposterior and lateral roentgenograms taken three days after injury, showing no bone involvement; *D* and *E*, taken two weeks, *F* and *G*, four weeks, and *H* and *I*, six weeks, after operation, showing no acute bone involvement, *J* and *K*, taken two months after operation, showing evidences of bone involvement; *L* and *M*, taken three months after operation, showing the phalanx completely regenerated.

Fig. 11 (case 5).—*A* and *B*, roentgenograms taken three weeks after the original injury. The incision was placed on the dorsum of the finger by the family physician. The air pocket indicates the location of the incision. The entire phalanx was destroyed. *C* and *D*, roentgenograms taken immediately after operation, showing a thin shell of base left intact. The patient was 25 years of age. *E* and *F*, roentgenograms taken two weeks after operation, showing regeneration of the phalanx; *G* and *H*, taken one month later; *I* and *J*, taken six weeks after operation, showing the major portion of the distal phalanx regenerated. The tuft is the only part missing. *K* and *L*, photographs taken one year later, showing no scar on the thumb and that the nail is regenerated

The distal phalanx has a dual blood supply, and removal of the major portion of the phalanx and preservation of the base will often give startling results in the regeneration of the phalanx.

The avulsed nail regenerates in a few weeks and hides the scar. The initial nail may be fissured, but eventually this is replaced by a normal nail. The infection clears, and the wound heals long before the nail regenerates.

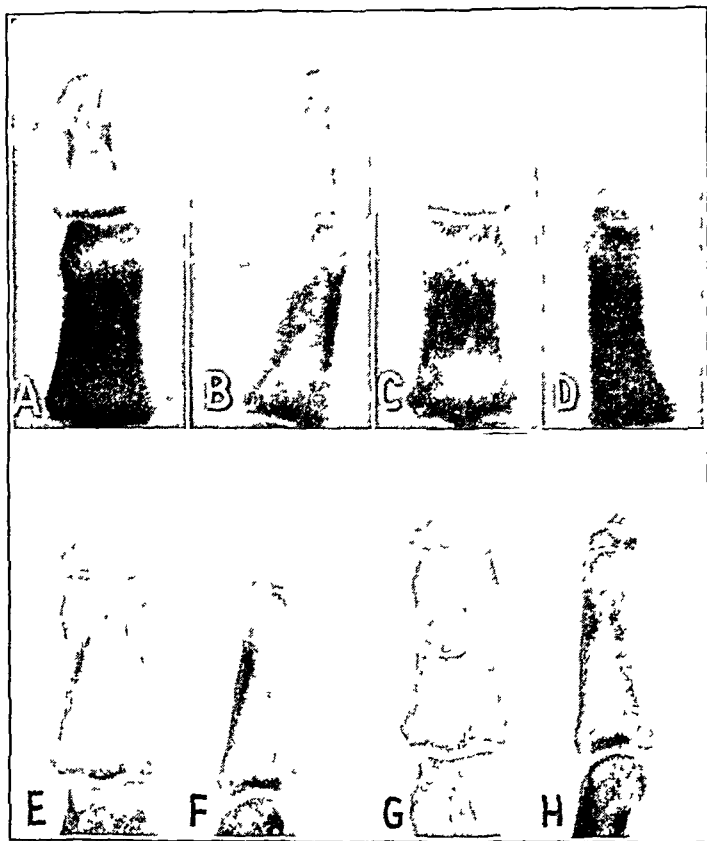


Fig. 12 (case 6).—*A* and *B*, roentgenogram of the index fingers revealing evidences of destruction of the distal phalanx and part of the head of the middle phalanx. There were evidences of suppurative tenosynovitis involving the deep flexor tendon. *C* and *D*, roentgenograms taken immediately after operation; *E* and *F*, taken five weeks after operation; *G* and *H*, taken eight weeks after operation.

Sensation remains intact, and the patient is restored to his or her industry or profession in a short time. Many a needleworker, engraver, pianist, violinist or even surgeon has had to give up his vocation because of impaired sensation or painful scars that have resulted from the fish mouth, hockey stick or median incisions.

REGENERATION OF SERUM ALBUMIN WITH HYDROLYZED PROTEIN IN CHRONIC HYPOPROTEINEMIA PRODUCED BY DIET

AN EXPERIMENTAL STUDY

ROBERT ELMAN, M.D.

LEO A. SACHAR, M.D.

ABRAHAM HORWITZ, M.D.

AND

HARRIET WOLFF, B.A.

ST. LOUIS

Search of the literature reveals no observations on the parenteral use of hydrolyzed protein in the regeneration of serum albumin in animals depleted of their plasma protein by diets deficient in protein. Such a diet has been used by many previous workers to produce hypoproteinemia. The most extensive studies were those of Weech and co-workers.¹ In studies of regeneration, these observers utilized intact proteins, such as meat, serum and casein, but did not employ hydrolyzed protein. Using the Weech diet, Mueller, Kemmerer, Cox and Barnes² showed regeneration values similar to those attained with casein when hydrolyzed protein was given by mouth. Increases in serum protein concentration were observed in operative patients with hypoproteinemia after the intravenous injection of the same hydrolyzed protein used in the experiments hereinafter described.³ The early experimental and clinical observations with hydrolyzed protein were summarized in a previous paper.⁴

This study was aided by grants from the Louis B. Beaumont Fund and Mead Johnson & Co.

From the Department of Surgery, Washington University School of Medicine and Barnes Hospital.

1. (a) Weech, A. A.; Goettsch, E., and Reeves, E. B.: *J. Exper. Med.* **61**:299, 1935. (b) Weech, A. A., and Goettsch, E.: *Bull. Johns Hopkins Hosp.* **63**:154 and 181, 1938; (c) **64**:425, 1939.

2. Mueller, A. J.; Kemmerer, K. S.; Cox, W. M., Jr., and Barnes, S. T.: *J. Biol. Chem.* **134**:573, 1940.

3. Elman, R.: *Ann. Surg.* **112**:594, 1940.

4. Elman, R., and Weiner, D. O.: Intravenous Alimentation, with Special Reference to Protein (Amino Acid) Metabolism, *J. A. M. A.* **112**:796 (March 4) 1939.

EXPERIMENTAL PROCEDURE

Thirteen dogs weighing 7 to 12 Kg. were placed on a controlled basal diet (protein and fat free) for five weeks. During the fourth week they were divided into three groups. Group 1 consisting of 4 dogs served as a control and received the basal diet during the entire period of five weeks. Group 2 consisting of 5 dogs received during the fourth week in addition to the basal diet a solution of 5 per cent hydrolyzed protein and 5 per cent dextrose intravenously. The solution was given daily for one week in an amount containing 4 Gm. protein digest (nitrogen, 0.5 Gm.) per kilogram of body weight per day. Group 3 consisting of 4 dogs received the same amount of hydrolyzed protein; this was added to the oral feeding.

TABLE 1.—*Serum Albumin and Nitrogen Balances*

Dog	Weight at Three Weeks (Kg.)	Serum Albumin (Gm. per 100 Cc.)			Change in Albumin During Fourth Week	Nitrogen Balance (Gm. per Week)		Percentage of Nitrogen Supplied by Protein Hydrolysate Utilized	
		Initial	After Three Weeks	After Four Weeks		After Five Weeks	During Third and Fifth Weeks (Average)		During Fourth Week
Group 1.—Controls Receiving No Protein Hydrolysate									
1	...	3.68	3.17	2.95	2.89	-0.22	
2	...	4.18	2.60	2.69	2.48	+0.09	-8.25	
3	...	4.13	3.05	2.60	2.72	-0.45	-7.12	
4	...	3.11	2.36	2.32	2.44	-0.04	-5.11	
Average	...	3.78	2.79	2.64	2.63	-0.15	
Group 2.—Protein Hydrolysate Given Intravenously During the Fourth Week Only									
5	8.0	3.85	2.51	3.29	3.69	+0.78	-7.3	+7.82	56
6	7.3	3.30	2.02	2.46	2.15	+0.44	-8.7	+5.57	57
7	5.6	3.92	2.61	3.07	2.68	+0.56	-6.0	+5.45	55
8	6.0	3.08	2.35	2.44	2.40	+0.09	-6.2	+5.18	54
9	6.2	3.39	2.01	2.27	2.25	+0.26	-9.1	+2.03	51
Average	6.6	3.51	2.30	2.71	2.63	+0.43	-7.5	+5.21	54.6
Group 3.—Protein Hydrolysate Given by Gavage During the Fourth Week Only									
10	8.0	3.68	2.63	2.79	3.09	+0.16	-5.4	+10.7	61
11	9.8	3.54	2.75	3.12	3.08	+0.37	-7.8	+12.7	64.5
12	9.5	4.25	2.52	2.99	3.08	+0.47	-6.3	+10.6	50.2
13	10.8	4.27	2.57	3.04	2.62	+0.47	-6.2	+12.2	50.8
Average	9.5	3.93	2.62	2.98	2.97	+0.37	-6.4	+11.5	56.6

Basal Diet.—The daily basal intake consisted of 1,000 cc. of 12.5 per cent sucrose and 0.05 per cent vitamin B complex concentrate⁵ in Ringer's solution. This solution was given twice daily by gavage. The daily caloric intake per dog was 500 calories. The nitrogen intake while a dog was being given the basal diet (owing almost entirely to the content of the vitamin B complex concentrate) was only 0.07 Gm. per day. Water was allowed ad libitum, but no other fluids or foods were given.

Hydrolyzed Protein.—The hydrolysate⁶ used in these experiments was a purified hydrolysate of casein and pork pancreas consisting of amino acids and polypeptides. It was nonantigenic, and its nitrogen content was 12.5 per cent. When

5. The vitamin B complex concentrate (Labco) used in three experiments obtained from the Borden Company, Bainbridge, N. Y.

6. The hydrolyzed protein (Amigen) used in these experiments was furnished by Mead Johnson & Co., Evansville, Ind.

it was given by mouth, the powder was simply added to the gavage feeding given as described.

Parenteral Injection.—Parenteral administration was carried out by continuous injection over a period of six to eight hours into the veins of the extremities. The dogs were unanesthetized and suspended in a canvas frame. When the solution entered at the stated rate, no significant symptoms developed during the venoclysis. Solutions used were prepared by dissolving the hydrolyzed protein and dextrose in hot freshly distilled water to make a solution containing 5 per cent of each. This solution was then passed through a Berkfeld filter into sterile bottles and sterilized by immersion in boiling water for thirty minutes. In dogs receiving this mixture parenterally, the amount of carbohydrate equivalent to that contained in the solution was subtracted from the basal diet so that the carbohydrate intake remained constant.

Studies of Nitrogen Balance.—All dogs were kept in individual metabolism cages. The feces under the conditions of the experiment were scanty and infrequent; the nitrogen content of these was measured in a few cases but found to be constant and so slight that they were not saved for further analysis. During the third, fourth and fifth weeks of the experiment the twenty-four hour urine

TABLE 2.—Average Serum Globulin Concentration *

	Dogs	Initial	After One Week	After Three Weeks	After Four Weeks	After Five Weeks
Group 1.....	5	2.30	2.24	2.32	2.42	2.49
Group 2.....	4	2.51	2.81	2.69	2.58	2.70
Group 3.....	4	2.36	2.31	2.59	2.52	2.42
Average.....	13	2.39	2.45	2.54	2.51	2.55

* Values are given in grams per hundred cubic centimeters.

was collected in receptacles containing thymol as a preservative and sufficient acid to neutralize ammonia. The daily volume of urine was carefully measured and combined for each metabolism period of one week before analysis. In some cases, however, each day's urine was analyzed separately.

Blood Samples.—Blood for chemical analysis was obtained from the external jugular vein, care being taken to obtain a minimum of stasis. Samples were taken at the start of the experiment after one, three, four and five weeks.

Analytic Procedures.—Determinations of total serum proteins and serum albumin were done in duplicate by measuring the nitrogen content of a suspension of the serum in a solution of sodium chloride. The micro-Kjeldahl and titration procedures were those described by Sobel, Yuska and Cohen.⁷ Separation of the albumin from the globulin fraction was effected by the method of Campbell and Hanna.⁸ Urinary nitrogen was determined by the micro-Kjeldahl procedure.

FINDINGS

On a basal diet consisting entirely of water, electrolytes, sucrose and vitamin B complex concentrate, with practically no nitrogen, dogs exhibited a progressive fall in the albumin fraction of the blood almost

7. Sobel, A.; Yuska, H., and Cohen, J.: J. Biol. Chem. **118**:443, 1937.

8. Campbell, W. R., and Hanna, M. I.: J. Biol. Chem. **119**:15, 1937.

entirely like that of previous observations,⁹ in which other types of low or nonprotein diet were used. As in the previous studies there was little significant change in the concentration of globulin (table 2). The total fall during the first three weeks amounted to about 30 per cent of the initial value. During the fourth and fifth weeks the albumin concentration of the control group (1) continued to fall but to a lesser degree.

During the week in which the dogs (group 2) were given the protein hydrolysate intravenously, there was a definite increase in the serum albumin concentration amounting to an average of 0.43 Gm. per hundred cubic centimeters, or 18.7 per cent above the depletion level. The albumin increase in the dogs (group 3) receiving the protein hydrolysate

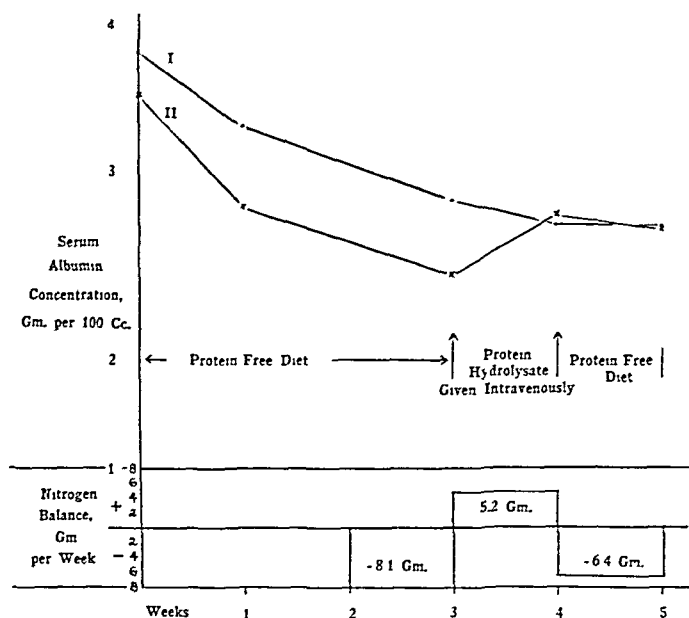


Chart 1.—Average serum albumin changes in dogs given a protein-free diet. I, control dogs, untreated; II, dogs given protein hydrolysate intravenously during the fourth week. Data on nitrogen balance is given for the latter. Note the drop in albumin concentration in both curves and the rise in curve II accompanied by a positive nitrogen balance during the week of treatment with protein hydrolysate.

by mouth was 0.37 per cent, or 14.1 per cent of the depletion value. Thus it is evident that the protein hydrolysate produces about the same rise in the serum albumin whether the material is given intravenously or by mouth.

The studies of nitrogen balance are especially significant and were analyzed to determine the efficiency of the protein hydrolysate, i. e., what

9. Elman, R., and Heifetz, C.: *J. Exper. Med.* **73**:417, 1941. Weech, Goettsch and Reeves.^{1a}

part of the amount given was actually retained. The calculation was made as follows: The nitrogen output of each animal during the third and fifth weeks was averaged and taken as the nitrogen output due to endogenic metabolism. During the fourth week (i. e., when the protein hydrolysate was administered), the nitrogen output was of course much higher. To determine the portion originating from the protein hydrolysate, the endogenic nitrogen value was subtracted from the actual output of nitrogen during this week. This figure represented the amount of nitrogen appearing in the urine supplied by the protein hydrolysate. When this was subtracted from the amount of nitrogen administered, a

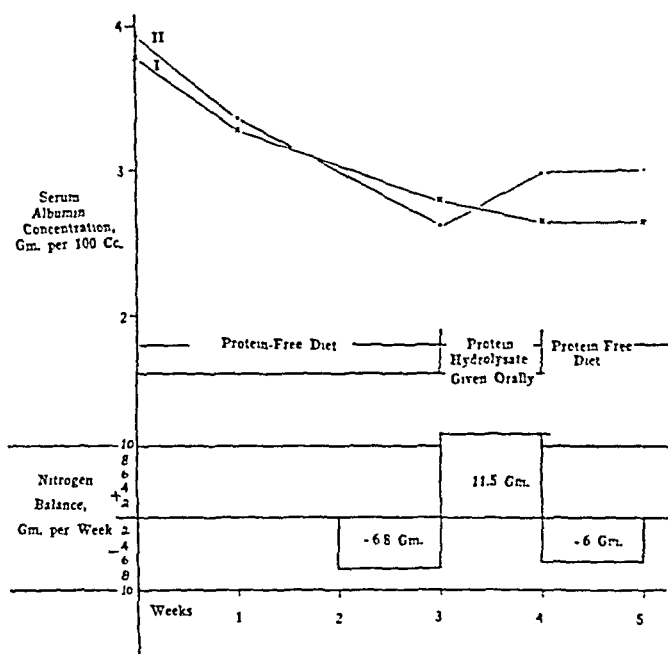


Chart 2.—Average serum albumin changes in dogs given a protein-free diet. I, control dogs, untreated; II, dogs receiving protein hydrolysate by mouth during the fourth week. Data on nitrogen balance is given for the latter. Note the drop in albumin concentration in both curves and the rise in curve II accompanied by a positive nitrogen balance during the week of treatment with protein hydrolysate.

value was obtained representing the amount of nitrogen retained by the dogs. As can be seen from chart 1, an average of 54.6 per cent of nitrogen supplied by the protein hydrolysate was retained in the dogs receiving the hydrolysate parenterally, while 56.6 per cent was retained by those receiving it by mouth. From this it is obvious that there is little significant difference in the percentage of nitrogen retained whether the protein hydrolysate is given by mouth or intravenously.

Another interesting calculation was made on the relation between the increase of the serum albumin and the amount of nitrogen retained during the week of therapy with the protein hydrolysate. By assuming that the plasma volume is one twentieth of the body weight, it is possible to determine the amount of total plasma albumin which was regenerated during the week of treatment. This figure is then compared with the amount of nitrogen retained. For example, dog 6 gained 1.60 Gm. of serum albumin (estimated plasma volume of 365 cc. \times .44), or 0.256 Gm. of nitrogen, during the week of therapy. The nitrogen retained during this week was 5.57 Gm. The proportion is 0.256:5.57, or 2.18

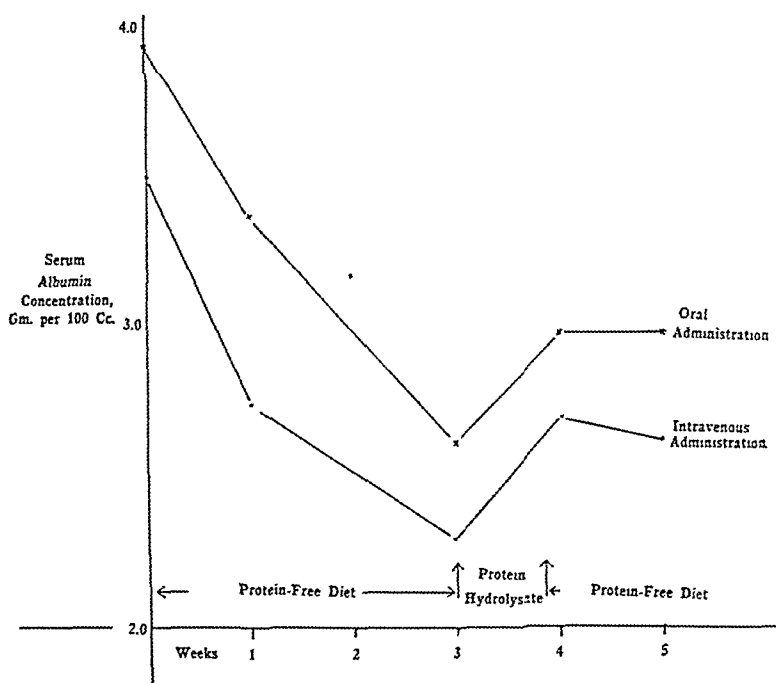


Chart 3.—Comparison of changes in the average serum albumin concentration of dogs receiving protein hydrolysate enterally and parenterally. Note the similarity of the two curves.

per cent. In other words, but a small percentage (the average was 3.5) of the nitrogen retained actually went into the manufacture of serum albumin. To put the matter another way—of the nitrogen retained during the period of treatment with the protein hydrolysate about thirty times as much went to the tissue protein as that which could be accounted for by the increase in the serum albumin.

COMMENT

It seems evident from the data presented in these experiments that the nitrogen in an almost completely hydrolyzed protein leads to about the same degree of regeneration of serum albumin whether given by

mouth or by vein. Moreover, observations of nitrogen balance indicate that the same amount of nitrogen is retained whether the intravenous or the oral route is employed.

The rise in serum albumin averaged about 0.4 Gm. per hundred cubic centimeters during the week of therapy. This is somewhat larger than similar studies already mentioned,¹⁰ in which, however, somewhat smaller doses of protein were given. Nevertheless, it is disappointing from the therapeutic point of view that such a large dose of the protein hydrolysate as 4 Gm. per kilogram per day was needed to achieve this rise. On the other hand, calculations noted before suggest that only a small proportion of the retained nitrogen can actually be utilized for the regeneration of serum albumin; on such a basis it is not surprising that large amounts must be given to effect a significant increase in the concentration of the plasma albumin. It may well be that the difficulties often experienced in correcting severe degrees of nutritional hypoproteinemia have been due to the fact that insufficient amounts of protein were employed.

SUMMARY

In dogs receiving only sucrose and vitamin B concentrate in Ringer's solution, a progressive fall in the concentration of serum albumin develops, averaging 1.2 Gm. per hundred cubic centimeters, or about 30 per cent of the initial value, in three weeks. The serum globulin remains unchanged.

Administration to these protein-depleted dogs of 4 Gm. per kilogram of body weight per day of hydrolyzed protein for one week leads to positive nitrogen balance and appreciable increase (regeneration) of serum albumin (0.4 Gm. per hundred cubic centimeters).

There is no significant difference in the proportion of nitrogen retained or in the amount of serum albumin regenerated whether the hydrolysate is given by mouth or intravenously.

Study of the data on nitrogen balance indicates that 96.5 per cent of the nitrogen retained by animals during the week of therapy with the protein hydrolysate is utilized for the replenishment of the tissue proteins, while only about 3.5 per cent can be accounted for in the replenishment of serum albumin.

10. Weech and Goettsch.^{1b} Mueller, Kemmerer, Cox and Barnes.²

HYPOPROTEINEMIA IN SURGICAL DISEASES

RELATION OF THE SERUM PROTEIN LEVEL TO HEPATIC FUNCTION AND THE INFLUENCE OF THE TRANSFUSION OF ASCITIC FLUID

HARRY A. DAVIS, M.D.

AND

PAUL L. GETZOFF, M.D.

NEW ORLEANS

The significance of the hypoproteinemic state with regard to operation has been recognized only during the past few years. As a result, a considerable amount of investigation, experimental and clinical, has been carried out on the problems associated with the causation and the therapy of hypoproteinemia. These problems at first appeared to be simple, but with a greater understanding of the syndrome associated with hypoproteinemia came the realization that many questions still remain unanswered. Patients with hypoproteinemia exhibit puzzling variations in their responses to treatment. The problem is not merely one of protein replacement. It is our purpose here to present a classification of the various forms of hypoproteinemia, to examine the causative factors involved in various hypoproteinemic states and to describe the results of the transfusion of ascitic fluid in this group of patients.

CLASSIFICATION

Any classification is useful only so far as it tends to clarify the factual knowledge on which it is based. To be accurate it must rest on a substrate of proved facts. The classification hereinafter presented is based on present day knowledge of the physiology of plasma protein formation. The central site of formation of the plasma proteins is the liver. The evidence in this regard appears to be least equivocal with respect to plasma fibrinogen. This is formed entirely in the liver. If the liver is removed or if it is severely damaged by phosphorus or chloroform, there occurs a marked fall in the plasma fibrinogen. With regard to albumin, the evidence points strongly toward the liver as the only site of formation. Thus, partial hepatectomy or the production of

From the Departments of Surgery and Urology, Louisiana State University School of Medicine, and the Charity Hospital.

an Eck fistula results in a lowering of the plasma albumin level. Plasma globulins, on the other hand, represent a mixture of proteins, the origins of which are probably varied. Undoubtedly, most of them are formed in the liver. But it is likely that certain of them may be produced by many other tissues and that the reticuloendothelial system is an important site of formation. The replacement of the plasma proteins takes place from two sources: (1) exogenic—from ingested food; (2) endogenic—from the reserve store of plasma protein-building material.

In the final analysis, of course, the plasma protein level is dependent on the continued ingestion of material which can be utilized for the formation of plasma proteins. The first evidence brought forward to show that the diet is a potent factor in the regeneration of depleted

TABLE 1.—*Classification of Hypoprotecinemia in Relation to Causation*

Type of Hypoproteinemia	Causes of Experimental Hypoproteinemia	Causes of Clinical Hypoproteinemia
1. Prehepatic	Low protein diet; Eck fistula	Malnutrition; anorexia; obstructive lesions of the esophagus or the pylorus; achylia and achlorhydria; gastrectomy; diarrhea; jejunostomy; ileostomy; jejunocolic fistula
2. Hepatic	Partial hepatectomy; chloroform and phosphorus poisoning of the liver; production of abscesses	Hepatitis; acute atrophy of the liver; cirrhosis of the liver; chronic atrophy of the liver (Thompson, McQuarrie and Bell ²³); chloroform poisoning of the liver; tuberculous of the liver; infection with or without abscess formation; thyrotoxicosis
3. Posthepatic	Plasmapheresis; hemorrhage; plasma loss by injections of bile, burns, trauma, freezing and dehydration	Chronic loss of blood; helminthic infection, including hookworm disease; chronic protein loss, e. g., from nephrosis and suppurating wounds; repeated removal of ascitic fluid; acute plasma loss in burns, trauma and various types of peritonitis; chronic bile peritonitis; dehydration

plasma proteins was that of Kerr, Hurwitz and Whipple.¹ The proteins in the food influence not only the regeneration of plasma albumin but also that of plasma globulin.² After the amino acids reach the liver by the portal vein from the intestinal tract, they are built partly into proteins and partly into plasma protein-building material. A portion of this synthesized material is placed in the reserve store of plasma proteins. These stores lie mainly in the liver but are present also in

1. Kerr, W. J.; Hurwitz, S. H., and Whipple, G. H.: Regeneration of Blood Serum Protein: II. Influence of Diet upon Curve of Protein Regeneration Following Plasma Depletion, *Am. J. Physiol.* **47**:370-378 (Dec.) 1918.

2. Holman, R. L.; Mahoney, E. B., and Whipple, G. H.: Blood Plasma and Protein Regeneration Controlled by Diet: I. Liver and Casein as Potent Diet Factors, *J. Exper. Med.* **59**:251-267 (March) 1934. Pommerenke, W. T.; Slavin, H. B.; Kariher, D. H., and Whipple, G. H.: Blood Plasma Protein Regeneration Controlled by Diet: Systematic Standardization of Food Proteins for Potency in Protein Regeneration, *ibid.* **61**:261-282 (Feb.) 1935.

many other tissues. In these reserves are placed the precursors of the plasma proteins, although a portion is stored as fully formed protein, which is then available instantly in times of stress. It is apparent, therefore, that the cycle of plasma protein formation revolves around the liver, both from the viewpoint of formation and from that of storage. With these facts in mind, we have classified hypoproteinemia into three types: (1) prehepatic hypoproteinemia; (2) hepatic hypoproteinemia, and (3) posthepatic hypoproteinemia (table 1). Hypoproteinemia of the prehepatic type is caused by interference with adequate intake, digestion or absorption of plasma protein-building materials. In this type the ability of the liver to form plasma proteins is not affected, but the supply of protein-building material is inadequate. There occurs, in other words, a prehepatic deviation of the material necessary for the building of plasma protein. Hypoproteinemia of the hepatic type results from the inability of the liver itself to build the plasma proteins, despite the fact that adequate supplies of plasma protein-building material are received from the intestine. In posthepatic hypoproteinemia there is an adequate formation of proteins by the liver, but an abnormal source of loss of plasma proteins is present. This classification will now be examined in the light of the causation of the hypoproteinemic state as seen in man and in the experimental animal.

CAUSATIVE FACTORS

One must not confuse the causation of hypoproteinemia with the causation of the secondary manifestations of that state, e. g., edema, since it is possible to have one without the other. In the prehepatic type of hypoproteinemia, the causative factors are those producing inadequate intake, deficient digestion or insufficient absorption of plasma protein-building material. Thus there is nutritional edema or famine edema,³ hypoproteinemia associated with inadequate intake due to a benign or a malignant stricture of the esophagus, reduction of food intake due to indigestion or to pain associated with a gastric ulcer or gastric carcinoma⁴ or to vomiting due to pyloric stenosis. Another cause is inadequate digestion of protein due to previous gastrectomy⁵ or to achlorhydria associated with diffuse toxic goiter⁶ or with pernicious

3. Schittenhelm, A., and Schlecht, H.: Ueber die Oedemkrankheit, *Ztschr. f. d. ges. exper. Med.* **9**:1-103, 1919.

4. Sisto, P.: La forma idropico-anemica del cancro dello stomaco, *Minerva med.* **1**:267-273 (March) 1937.

5. Netoušek, M.: Observation d'un cas d'oedème généralisé chez un ancien réséqué d'estomac. Disparition des oedèmes après opothérapie gastrique, *Arch. d. mal. de l'app. digestif* **25**:984-986 (Nov.) 1935.

6. Mussio-Fournier, J. C.; Castiglioni, C. A., and Anido, J. B.: Oedèmes mous, hypoprotéinémie et anachlorhydrie chez une malade atteinte de goître exophtalmique, *Rev. neurol.* **1**:756-760 (May) 1934.

anemia.⁷ Deficient intake of protein may occur in the aged owing to anorexia and may lead to hypoproteinemia.⁸ Endemic forms of edema are also due to low protein diets and have been observed in various parts of the world, e. g., in Annam, part of French Indochina.⁹ Inadequate absorption of food may occur as a result of diarrhea and may produce hypoproteinemia, particularly in children.¹⁰ Similarly, defective absorption of food may occur in the presence of jejunostomy, ileostomy or cecal fistula,¹¹ tuberculosis of the small intestine,¹² regional enteritis¹³ and jejunocolic fistula.¹⁴ Pain during defecation as a result of a benign or a malignant stricture of the rectum may cause the patient to reduce the intake of food so that hypoproteinemia develops. The use of poorly balanced diets by patients with diabetes can result in malnutrition and hypoproteinemia. In diabetes mellitus associated with hypoproteinemia, edema will occur only in the absence of acidosis.¹⁵ In the prehepatic type of hypoproteinemia, does a deficient intake of protein provide an adequate explanation of the causation? The contention of Bloomfield¹⁶ that additional unknown factors also are involved has been supported by later investigators.¹⁷ However, it should be pointed out that some con-

7. Meulengracht, E.; Iversen, P., and Nakazawa, F.: Edema and Water Excretion in Pernicious Anemia, *Ugesk. f. læger* **89**:1020-1023 (Nov. 10) 1927.

8. Durand, P.: Les oedèmes par carence alimentaire chez les vieillards, *Rev. gén. de clin. et de thérap.* **49**:855-856 (Dec.) 1935.

9. Normet, L.: Renseignements complémentaires sur la pathogénie de la bouffissure d'Annam, maladie de carence, *Bull. Acad. de méd., Paris* **117**:239-242 (Feb.) 1937.

10. Ariztia, A.: Sindromas edematosos con hipoproteinemia en el niño menor, *Rev. chilena de pediat.* **9**:1-13 (Jan.) 1938. Schwarzenberg, L. J., and Cousino, J.: Dos casos de edemas generalizados con hipoproteinemia, *ibid.* **9**:747-755 (Sept.) 1938.

11. Wolferth, C. C.: Inanition Edema Associated with Alimentary Disturbances in Adults, *M. Clin. North America* **8**:785-801 (Nov.) 1924.

12. Landis, E. M., and Leopold, S. S.: Inanition Edema Associated with Tuberculous Enteritis, *J. A. M. A.* **94**:1378-1381 (May 3) 1930.

13. Casten, D.: Nutritional Disturbances in Regional Enteritis, *Surgery* **6**:708-716 (Nov.) 1939.

14. deNavasquez, S.: Nutritional Edema as a Complication of Jejunocolic Fistula, *Brit. J. Surg.* **28**:468-471 (Jan.) 1941.

15. Peters, J. P.; Bulger, H. A., and Eisenman, A. J.: The Plasma Proteins in Relation to Blood Hydration: II. In Diabetes Mellitus, *J. Clin. Investigation* **1**:451-472 (June) 1925.

16. Bloomfield, A. L.: The Effect of Restriction of Protein Intake on the Serum Protein Concentration of the Rat, *J. Exper. Med.* **57**:705-720 (May) 1933.

17. (a) Weech, A. A.; Goettsch, E., and Reeves, E. B.: Nutritional Edema in the Dog: I. Development of Hypoproteinemia on a Diet Deficient in Protein, *J. Exper. Med.* **61**:299-317 (March) 1935. (b) Youmans, J. B.; Bell, A.; Donley, D., and Frank, H.: Endemic Nutritional Edema: II. Serum Proteins and Nitrogen Balance, *Arch. Int. Med.* **51**:45-61 (Jan.) 1933.

fusion has arisen here between the causation of hypoproteinemia and the causation of the secondary manifestations, such as edema. Hypoproteinemia of the prehepatic type seems to be definitely related to an inadequate supply of plasma protein-building materials to the liver, since the provision of a high protein diet causes the disappearance of hypoproteinemia. However, other factors besides hypoproteinemia are probably involved in the causation of edema since this does not always disappear simultaneously with a rise in the serum protein level.^{17b}

As has been stated previously, hepatic hypoproteinemia results from the inability of the liver to synthesize plasma proteins despite an adequate supply of precursor material. Intrinsic disease of the liver may be associated with edema.¹⁸ More recently, hypoproteinemia and edema have been noted in association with extreme tuberculous involvement of the liver,¹⁹ with subacute yellow atrophy of the liver,²⁰ with syphilis of the liver,²¹ with portal cirrhosis of the liver²² and with idiopathic liver atrophy.²³ The association of hypoproteinemia and edema with intrinsic disease of the liver appears to be well established. Nevertheless, edema without hypoproteinemia has been observed in acute yellow atrophy of the liver²⁴ and in catarrhal jaundice.²⁵

Extrahepatic infections may result in hypoproteinemia. It has been shown that the production of an abscess will inhibit protein regeneration by the liver.²⁶ Another important factor is the loss of protein into the

18. Schrumpf, A.: Ein Fall von Leberinsuffizienz mit Ödemen, *Klin. Wchnschr.* **9**:2444 (Dec. 27) 1930.

19. May, E., and Braillon, J.: Grande anasarque primitive: Hépatite hypertrophique graisseuse tuberculeuse sans lésions rénales, *Bull. et mém. Soc. méd. d. hôp. de Paris* **50**:1597-1602 (Dec. 10) 1934.

20. Caroli, J.; Cachera, R., and Deparis, M.: Les formes hydropiques de l'ictère catarrhal, *Paris méd.* **1**:435-439 (May 16) 1936.

21. Weech, A. A.: Nutritional Edema, *Internat. Clin.* **2**:223-248 (June) 1936.

22. Baumel, J., and Serre, H.: Le syndrome hydropigène dans les maladies du foie, *Rev. méd.-chir. d. mal. du foie* **12**:65-121 (March-April) 1937. Eisenfarb, J.: Anémie hyperchrome au cours d'un ictère grave. Contribution à l'étude de l'anémie hyperchrome et de l'oedème au cours des affections parenchymateuses aiguës du foie, *ibid.* **13**:271-281 (July-Aug.) 1938.

23. (a) Thompson, W. H.; McQuarrie, I., and Bell, E. T.: Edema Associated with Hypogenesis of Serum Proteins and Atrophic Changes in the Liver, *J. Pediat.* **9**:604-619 (Nov.) 1936. (b) Myers, W. K., and Taylor, F. H. L.: Hypoproteinemia Probably Due to Deficient Formation of Plasma Proteins, *J. A. M. A.* **101**:198-200 (July 15) 1933.

24. Loeper, M.; Roy, A.; Perreau, P., and Varay, M.: L'oedème des hépatites ictériques graves, *Bull. et mém. Soc. méd. d. hôp. de Paris* **52**:1173-1180 (July 13) 1936.

25. Cernich, R.; Palazón, J. M., and de Lellis, J. D. M.: Hepatitis ictérogena con edema, *Semana méd.* **2**:1008-1010 (Oct. 8) 1936.

26. Madden, S. C.; Winslow, P. M.; Howland, J. W., and Whipple, G. H.: Blood Plasma Protein Regeneration as Influenced by Infection, Digestive Disturbances, Thyroid and Food Proteins, *J. Exper. Med.* **65**:431-454 (March) 1937.

site of suppuration. The diminution of liver function so frequently associated with thyrotoxicosis may explain in part the occurrence of hypoproteinemia and edema in a patient suffering from toxic diffuse goiter.⁶

The posthepatic type of hypoproteinemia results from a loss of fully formed plasma protein from the body. This may be produced experimentally by plasmapheresis, hemorrhage, subcutaneous or intraperitoneal injections of bile,²⁷ burns, trauma and freezing. Clinically, a variety of conditions may lead to protein loss. Protracted loss of blood is an occasional factor. Hypoproteinemia and edema have been noted in association with the helminthic types of anemia, particularly ankylostomiasis and intestinal bilharziasis.²⁸ Loss of plasma protein into localized areas as a result of burns or trauma will cause hypoproteinemia which may be unrecognized until fluids are administered and edema occurs. Infections associated with suppuration are an important cause of hypoproteinemia of the posthepatic type. The amount of protein which is lost in pus is considerable and has been estimated to vary from 8.1 to 21 Gm. per hundred cubic centimeters of total protein and from 4.6 to 11.5 Gm. per hundred cubic centimeters of albumin.²⁹ This would explain in part the occurrence of hypoproteinemia and edema in appendical abscess,³⁰ peritonitis,³¹ infected burns,³² empyema^{29b} and suppurating lung cysts.³³ Diarrhea, if associated with loss of blood and pus, may lead to hypoproteinemia and edema, e. g., in chronic ulcerative colitis³⁴ and in dysentery.³⁵ In severe dehydration, a breaking

27. Harkins, H. N.; Harmon, P. H., and Hudson, J. E.: Lethal Factors in Bile Peritonitis: I. "Surgical Shock," *Arch. Surg.* **33**:576-608 (Oct.) 1936.

28. Salah, M.: Mechanism of Oedema in Helminthic Anemias, *Tr. Roy. Soc. Trop. Med. & Hyg.* **31**:431-436 (Jan.) 1938.

29. (a) Jones, C. M.; Eaton, F. B., and White, J. C.: Experimental Post-operative Edema, *Arch. Int. Med.* **53**:649-674 (May) 1934. (b) Mauriac, P.: Oedème et suppuration pleurale tuberculeuse, *Presse méd.* **44**:1215-1216 (July 25) 1936.

30. Meyer, O. O.: Generalized Edema After Surgery, with Case Report, *Wisconsin M. J.* **33**:427-431 (June) 1934.

31. Curphey, W. C., and Orr, T. G.: Edema in Surgical Patients, *Surgery* **1**: 589-594 (April) 1937. Jones, Eaton and White.^{29a}

32. Clavelin, M., and Hugonot, M.: Oedème généralisé chez un brûlé: Contribution à la pathogénie des oedèmes, *Bull. et mém. Soc. méd. d hôp. de Paris* **52**:1444-1449 (Nov. 16) 1936.

33. Troisier, J.; Bariety, M., and Hautefeuille, E.: Double kyste pulmonaire suppuré. Cachexie oedémateuse curable, *Bull. et mém. Soc. méd. d. hôp. de Paris* **54**:417-426 (March 21) 1938.

34. Barga, J. A., and Brown, P. W.: A Complication of Chronic Ulcerative Colitis Hitherto Not Described, *M. Clin. North America* **18**:529-533 (Sept.) 1934.

35. Iskander, F.: Post-Dysenteric Edema in Children, *J. Egyptian M. A.* **18**:134-137 (Feb.) 1935.

down of the plasma proteins occurs with a resultant hypoproteinemia.³⁶ It should be remembered that all infections, particularly those associated with suppuration, may interfere with protein regeneration by the liver and may thus accentuate hypoproteinemia, if present.

PHYSIOLOGIC EFFECTS OF HYPOPROTEINEMIA

The physiologic effects of hypoproteinemia are readily understood when consideration is given to the functions of the serum proteins. If the discussion is limited to albumin and globulin, the proteins may be said to serve three main functions: (1) maintenance of the osmotic pressure of the blood; (2) maintenance of the hydrogen ion concentration of the blood at normal levels; (3) provision of food material in times of stress. The maintenance of the osmotic pressure of the blood is of great importance in the distribution of fluid between the blood stream and the interstitial tissue spaces. The osmotic pressure of the normal serum is between 21 and 29 mm. of mercury. The osmotic pressure of 1 Gm. of albumin is 5.5 mm. of mercury and of 1 Gm. of globulin, 1.4 mm. of mercury. As the concentration of the serum proteins is increased, each gram exerts more osmotic pressure than it did in more dilute solutions.³⁷ According to the Starling hypothesis, the distribution of fluids between the blood stream and the extravascular spaces is dependent on the interaction of the hydrostatic pressure of the blood and the osmotic pressure of the serum proteins. From this standpoint, albumin is most effective. Since, however, the rate of regeneration of albumin is slower than that of globulin or fibrinogen, it is found that albumin values tend to be low in hypoproteinemia, while those of globulin are reduced, normal or even elevated. This dissociated type of hypoproteinemia, i. e., a lowered albumin level with an elevated globulin level, is most often found in suppurative conditions of long standing.

The effects produced by a reduction of the protein content of the serum will be dependent on the extent and the rate of reduction. The influence of the extent of reduction of proteins is exemplified by the appearance of edema at the critical level, which, according to Moore and Van Slyke,³⁸ is, 5.5 ± 0.3 Gm. per hundred cubic centimeters for total serum proteins and 2.5 ± 0.2 Gm. per hundred cubic centimeters

36. Maes, U., and Davis, H. A.: Fluid Replacement in Surgical States with Particular Reference to Transfusion of Ascitic Fluid: A Clinical and Experimental Study, *Arch. Surg.* **42**:453-479 (March) 1941.

37. Fishberg, E. H.: The Relations of the Serum Proteins and Lipids to the Osmotic Pressure, *J. Biol. Chem.* **81**:205-214, 1929. Verney, E. B.: The Osmotic Pressure of the Proteins of Human Serum and Plasma, *J. Physiol.* **61**:319-328 (June) 1926.

38. Moore, N. S., and Van Slyke, D. D.: The Relationships Between Plasma Specific Gravity, Plasma Protein Content and Edema in Nephritis, *J. Clin. Investigation* **8**:337-355 (April) 1930.

for serum albumin. At this level, the osmotic pressure of the blood is so reduced that the hydrostatic pressure of the blood exceeds it and water passes into the extravascular tissue spaces. The influence of the rate of reduction of the serum proteins is illustrated by the fact that their rapid removal by plasmapheresis may produce "hypoproteinemic" shock.³⁹ This is due to a reduction of plasma volume and thereby of the blood volume. Clinical analogies to the hypoproteinemic shock of animals are seen in conditions of plasma loss associated with trauma, burns and peritonitis.

TABLE 2.—*Electrocardiographic Studies of Hypoproteinemia*

Patient and Sex	Race and Age, Yr.	Diagnosis	Serum Proteins, Gm. per 100 Cc.	Electrocardiogram
W. B. ♂	W 14	Chronic osteomyelitis; acute glomerulonephritis	3.65	No change
A. B. ♀	W 65	Carcinoma of the rectum	5.0	Slight axis deviation; slight depression of ST segment in leads I and II; R-2 notched on downstroke near base; electrocardiogram suggested overwork of the left ventricle but no evidence of organic disease
E. E. ♀	N 21	Syphilitic cirrhosis of the liver	5.2	No change
J. D. ♂	W 55	Calculus pyonephrosis	6.3	Definite electrocardiographic evidence of myocardial disease, suggestive of old posterior infarct
L. N. ♀	N 60	Carcinoma of the stomach	3.72	Left axis deviation; all complexes reduced in amplitude; definite electrocardiographic evidence of myocardial disease
J. C. ♂	N 49	Amebic colitis	5.7	Left axis deviation; P waves wide and notched; low T waves in leads I and II; definite electrocardiographic evidence of myocardial disease
R. J. ♀	N 27	Toxemia of pregnancy	4.63	Low T waves; ST segments in leads I, II and IV depressed; electrocardiogram suggested toxic condition

Frequently, secondary anemia accompanies hypoproteinemia, but probably the same causative factors underlie both conditions. There are no data available as to the direct effects of hypoproteinemia on hematopoiesis, but it is possible that defective blood formation may result from an insufficient supply of protein-building material. Hypoproteinemia is associated with a reduced blood volume. Hypoproteinemia does not appear to affect cardiac function, since the electrocardiogram exhibits no characteristic changes (table 2). The blood pressure may be normal, elevated or lowered. Not infrequently it is lowered, and this may be

39. Whipple, G. H.; Smith, H. P., and Belt, A. E.: Shock as a Manifestation of Tissue Injury Following Rapid Plasma Protein Depletion: The Stabilizing Value of Plasma Proteins, *Am. J. Physiol.* 52:72-100 (May) 1920.

due to reduction of the blood volume. Hypoproteinemia affects the motor activity of the gastrointestinal tract, probably by permitting the occurrence of edema of the wall of the stomach and the intestines. Diminution in peristalsis of the stomach and delay in its emptying time have been noted.⁴⁰ This diminution of gastric peristalsis is difficult to reconcile with the finding of intestinal hyperperistalsis and diarrhea in hypoproteinemic dogs.^{29a} Clinically, one of us (H. A. D.) has noted diminished intestinal peristalsis in patients with hypoproteinemia such that adynamic ileus was simulated. This was relieved by blood transfusion. The relation of hypoproteinemia to liver function is of great interest. It will be noted that in our patients (table 3 and chart 1) hypoproteinemia was accompanied by a diminution in hepatic function.

The resistance of the liver to various forms of chemical injury and its ability to regenerate after injury are dependent on an adequate intake of protein-building material. In hypoproteinemia, not only is the liver more susceptible to injury, since its functional ability is reduced, but it is less able to regenerate after such injury because of the lowering of the reserves of protein precursors and formed protein.

It is of interest to compare the results of various types of liver function tests in hypoproteinemia. In dogs with hypoproteinemia, Elman and Heifetz⁴¹ found that the excretion of phentetiothalein sodium was diminished. The galactose tolerance test, however, revealed that the liver functioned normally in this respect. DeNavasquez¹⁴ noted that the dextrose and levulose tolerance tests for liver function revealed normal values in his patient with hypoproteinemia. The bromsulfalein test for liver function showed normal values in the patient with hypoproteinemia reported by Mussio-Fournier and co-workers.⁶ In our series of patients with hypoproteinemia (table 3), all, without exception, had marked reduction of liver function (intravenous hippuric acid test). These findings suggested that certain tests, e. g., the hippuric acid test, may be more sensitive indicators of the state of liver function than are other tests, e. g., galactose or dextrose tolerance tests, when used in patients with hypoproteinemia.

Extrahepatic infections appear to exert a reversible effect on the function of the liver. This is illustrated in chart 1. As the infection subsides, the return of liver function to normal occurs rapidly. There appears to be a "lag" period between these events (chart 1). There is a coincident rise in the level of the serum proteins. The relative rapidity

40. Mecray, P. M.; Borden, R. P., and Ravdin, I. S.: Nutritional Edema: Its Effect on the Gastric Emptying Time Before and After Gastric Operations, *Surgery* 1:53-64 (Jan.) 1937.

41. Elman, R., and Heifetz, C. J.: Experimental Hypoalbuminemia: Its Effect on the Morphology, Function, and Protein and Water Content of the Liver, *J. Exper. Med.* 73:417-430 (March) 1941.

TABLE 3.—*Relation of Serum Protein Level to Liver Function*

Patient	Sex	Age, Yr.	Clinical Condition	Total Serum Proteins, Gm. per 100 Cc.	Albumin, Gm. per 100 Cc.	Globulin, Gm. per 100 Cc.	Albumin-Globulin Ratio	Edema	Type of Hypo-proteinemia	Sources of Protein Defect
W. B.	M	W	14							
R. J.	F	N	21	3.65	1.36	2.29	0.59:1	0.27	Hepatic and post-hepatic	Diminished protein regeneration by the liver; loss of protein in urine and pus
H. B.	M	W	30	4.63	1.65	2.98	0.55:1	0.38	Hepatic and post-hepatic	Diminished protein regeneration by the liver; loss of protein in urine
W. S.	M	W	25	5.61	2.48	3.13	0.79:1	0.23	Hepatic and post-hepatic	Insufficient protein intake; diminished protein intake; diminished protein regeneration by the liver
A. B.	F	W	65	5.5	2.6	2.9	0.89:1	0.27	Hepatic and post-hepatic	Diminished protein regeneration by the liver; loss of protein in urine
L. N.	F	N	60	5.0	2.23	2.77	0.80:1	0.26	Hepatic and post-hepatic	Insufficient protein intake; diminished protein intake; diminished protein regeneration by the liver; loss of protein in ascitic fluid
E. E.	F	N	21	3.72	1.21	2.48	0.5:1	0.40	Hepatic and post-hepatic	Insufficient protein intake; diminished protein intake; diminished protein regeneration by the liver; loss of protein in rectum
J. D.	M	W	55	5.2	2.0	3.2	0.62:1	0.42	Hepatic and post-hepatic	Insufficient protein intake; diminished protein intake; diminished protein regeneration by the liver
				6.3	1.65	4.65	0.35:1	0.27	Hepatic and post-hepatic	Insufficient protein intake; diminished protein intake; diminished protein regeneration by the liver
										Loss of protein in the urine; diminished protein regeneration by the liver

J. C.	M	N	19	Amebic colitis	5.7	2 25	3.45	0 65	1	0 37	Pedal, Grade 1	Combined*	Insufficient protein intake and absorption, loss of protein in feces; diminished liver regeneration by the liver
J. P.	F	N	38	Pelvic abscess	5.21	0.27	Lower extremities, grade 2	Hepatic and post-hepatic	Loss of protein in pus from abscess; diminished protein regeneration by the liver
J. T.	F	N	24	Rectal stricture; anorexia	3.17	0.20	Lower extremities, grade 1	Combined*	Insufficient protein intake and absorption; diminished protein regeneration by the liver; loss of protein in feces	
M. L.	F	W	44	Pyonephrosis	5 10	0.396	Lower extremities, grade 2	Hepatic and post-hepatic	Loss of protein in urine; diminished protein regeneration by the liver	
E. W.	F	N	40	Tuberculous peritonitis; jejunostomy	4.99	0.343	Pedal, Grade 4	Combined*	Insufficient absorption of protein; loss of protein in peritoneal exudate; diminished protein regeneration by the liver	
E. S.	M	W	56	Cystitis and pyelonephritis	5 02	0.282	Lower extremities, grade 2	Hepatic and post-hepatic	Loss of protein in urine; diminished protein regeneration by the liver	
D. A.	M	W	61	Prostatic hypertrophy with urinary retention and infection	4 93	0.54	Pedal, grade 3	Combined*	Diminished intake of protein, loss of protein in pus, diminished protein regeneration by the liver	
E. V.	M	N	59	Carcinoma of the rectum, infection of the abdominal wall	5 8	0.30	Generalized, grade 1	Combined*	Deficient intake and absorption of protein, loss of protein in feces; diminished protein regeneration by the liver	
M. W.	M	N	27	Amebic colitis manition	4.67	2.4	2 27	1 05.1	0 30				

* Combination of prehepatic, hepatic and posthepatic types.

* Combination of prehepatic, hepatic and posthepatic types.

with which these processes occur suggests that at least in this type of hypoproteinemia there is little depletion of the protein reserves and that the effect of the infection is to render the liver less able to utilize adequately the stores of protein precursor material for protein formation. The duration of the hypoproteinemic state is significant since it has been shown that in dogs prolonged hypoproteinemia further diminishes the ability of the liver to form proteins.⁴²

It is difficult to reconcile these facts with the observations of other workers, who have found that patients with hepatic disease, e. g., portal cirrhosis and obstructive jaundice, may exhibit normal plasma protein levels.⁴²

The effect of hypoproteinemia on renal function is of interest. Due to prerenal deviation of water into the extravascular tissue spaces, a fall

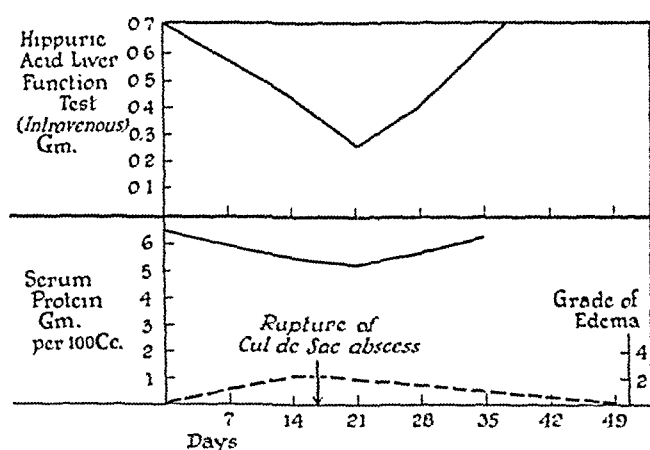


Chart 1.—Relation of serum protein level to hepatic function (patient J. P.).

in the amount of urine secretion occurs. There is, however, no true renal insufficiency. Occasionally, polyuria occurs in the presence of hypoproteinemia and edema. In animals, nephrosis with albuminuria, due to increased permeability of the glomerular capillaries, may follow a prolonged state of hypoproteinemia as a result of repeated plasmapheresis.⁴³

INFLUENCE OF HYPOPROTEINEMIA ON THE HEALING OF WOUNDS

The influence of hypoproteinemia on the healing of wounds is well known and therefore will be discussed only briefly here. Clinically, it may be observed that certain patients show difficulty in the healing of

42. Peters, J. P.; Eisenman, A. J., and Bulger, H. A.: The Plasma Proteins in Relation to Blood Hydration: I. In Normal Individuals and in Miscellaneous Conditions, *J. Clin. Investigation* **1**:435-450 (June) 1925.

43. Leiter, L.: Nephrosis, *Medicine* **10**:135-242 (May) 1931.

their operative wounds. The rate and the degree of growth of fibroblasts in wounds are increased by a high protein diet.⁴⁴ In patients with hypoproteinemia, wound healing is slow, and the tensile strength of the wound is low. The tendency to wound disruption is greater in this group of patients than it is in patients without hypoproteinemia.⁴⁵ The influence of hypoproteinemia seems to be limited to proliferation of the fibroblasts.

The growth of epithelium does not appear to be directly affected by hypoproteinemia. When accessory factors, such as wound infection, seroma and foreign bodies, are coexistent, the deleterious effect of hypoproteinemia on the healing of the wound is accentuated.

PATHOLOGIC EFFECTS OF HYPOPROTEINEMIA

The most obvious alterations of tissue structure are those resulting from the disturbance in water distribution, namely, edema. Thus, edema of the subcutaneous tissues and of various viscera, e. g., the lungs, the cardiac muscle, the gastrointestinal tract, the liver, the pancreas, the brain and the skeletal muscle may occur. Collections of fluid may be found in the peritoneal, the pleural, and the pericardial cavity.

Subcutaneous edema is usually first noted in the lower extremities. This is probably due to erect posture which favors the passage of fluid from the capillaries into the interstitial tissue spaces.⁴⁶ There does not appear to be a definite correlation between the presence of subcutaneous edema and edema of the viscera, since one may be absent while the other is present, owing to the fact that, while hypoproteinemia is the fundamental underlying cause, other factors are important in determining the time of onset and the distribution of edema. These factors are: (1) the amount of fluid intake; (2) the amount of basic ions, particularly sodium ions, dissolved in the body fluids (an increase in the amount of such ions tends to promote edema⁴⁷); (3) the presence of increased permeability of the capillaries (this may occur as a result of local capillary injury, e. g., from burns or trauma, or as a result of

44. Harvey, S. C., and Howes, E. L.: Effect of High Protein Diet on the Velocity of Growth of Fibroblasts in the Healing Wound, *Ann. Surg.* **91**:641-650 (May) 1930.

45. Thompson, W. D.; Ravdin, I. S., and Frank, I. L.: Effect of Hypoproteinemia on Wound Disruption, *Arch. Surg.* **36**:500-508 (March) 1938.

46. Youmans, J. B.; Wells, H. S.; Donley, D.; Miller, D. G., and Frank, H.: The Effect of Posture (Standing) on the Serum Protein Concentration and Colloid Osmotic Pressure of Blood from the Foot in Relation to the Formation of Edema, *J. Clin. Investigation* **13**:447-459 (May) 1934.

47. Fahr, G.; Kerkhof, A., and Giere, E.: Salt as a Factor in Edema Formation Following Plasmaphoresis, *Proc. Soc. Exper. Biol. & Med.* **29**:335-336 (Dec.) 1931. Liu, S. H.; Chu, H. I.; Li, R. C., and Fan, C.: Nutritional Edema: II. Effect of Alkali and Acids on Nitrogen Balance, Plasma Proteins and Edema, *ibid.* **29**:252-253 (Dec.) 1931.

general capillary injury, e. g., from infection); (4) diminution of tissue pressure (a normal degree of tissue tension or pressure is an important factor in limiting the outflow of fluid from the blood vessels, e. g., those of the lower extremities in the erect posture⁴⁰; a loss of tissue proteins as a result of malnutrition will lower the effective tissue pressure).

The tendency to edema formation seems to vary in different tissues. Thus, in conditions producing acute hypoproteinemia with little tissue protein deficit, there is a greater tendency toward the formation of ascites, hydrothorax and hydropericardium than toward edema of the subcutaneous tissues. Conversely, conditions which produce a depletion of both plasma and tissue protein, as in nutritional deficiency states, will show a higher incidence of subcutaneous edema. The walls of the gastrointestinal tract and the lungs appear to be more frequent sites of edema than do the other viscera. It is significant that these viscera normally have a looser tissue structure than do the liver, the kidneys, the brain or the heart.

Lesions of the tissues other than those associated with edema have been described. It must be remembered, however, that coexistent infection or tissue protein defect may be responsible for the lesions. According to Bablet and Normet,⁴⁸ in cases of the endemic form of nutritional edema occurring in Annam, examination of the heart at necropsy revealed partial disappearance of the cardiac muscle fibers and deformations of the muscle nuclei. It is probable that this was more the result of associated tissue protein defect than of hypoproteinemia. The same authors described the presence of fatty metamorphosis of the liver, affecting mainly the middle and central zones of the liver lobules with areas of necrosis in the midzonal areas. Fatty metamorphosis of the liver and brown atrophy of the heart have been described in hypoproteinemia.¹⁴ In a study of the causative factors concerned in the production of postoperative edema, moderate grades of liver necrosis were noted in animals (cats) in which abscesses had been produced.^{20a} More conclusive evidence of the effect of hypoproteinemia on the liver was presented by Elman and Heifetz,⁴¹ whose animals when maintained in the hypoproteinemic state for long periods revealed a loss of hepatic cell substance, an increased content of water in the liver and a diminution of liver function.

CLINICAL PICTURE OF HYPOPROTEINEMIA

The picture presented by these patients is subject to puzzling variations. Usually, such patients may be classified in one of three groups:

48. Bablet, J., and Normet, L.: Les lésions histopathologiques de la bouffissure d'Annam, *Bull. Acad. de méd., Paris* **117**:242-244 (Feb. 23) 1937.

(1) those with cryptic hypoproteinemia; (2) those with hypoproteinemia without edema; (3) those with hypoproteinemia with edema.

In the first group, hypoproteinemia is masked by coexistent dehydration. Examination of the blood reveals a normal or a slightly elevated serum protein level. The administration of fluids, particularly by the intravenous route, is promptly followed by the appearance of subcutaneous edema. At this time, examination of the blood reveals a definite lowering of the serum protein level. This group is composed of patients with diseases which interfere with the intake or absorption of proteins and of water, e. g., benign or malignant strictures of the esophagus, pyloric obstruction, severe diarrhea, or duodenal, jejunal and ileal fistulas.

TABLE 4.—*Hypoproteinemia Without Edema*

Patient and Sex	Race and Age, Yr.	Diagnosis	Serum Protein, Gm. per 100 Cc.	Type of Hypoproteinemia	Daily Fluid Intake		Daily Urinary Output, Cc.
					Oral, Cc.	Paren-teral, Cc.	
J. L. ♂	W 47	Duodenal ulcer with pyloric obstruction (vomiting)	4.77	Prehepatic	1,500-2,000	1,000	1,200-1,800
A. E. ♂	W 59	Carcinoma of the small intestine (hematemesis and melena)	4.42	Prehepatic and posthepatic	2,000	1,000-1,500
M. P. ♀	W 59	Dissecting aneurysm of the aorta (retroperitoneal hemorrhage; bilateral hydrothorax)	4.80	Posthepatic	3,000	1,000-2,000
M. P. ♀	W 73	Carcinoma of the kidney (continuous and severe hematuria)	5.11	Posthepatic	1,000-2,000	1,000-1,500

Hypoproteinemia in patients of the second group is not accompanied by edema of the subcutaneous tissues and is somewhat difficult to recognize. Its presence is suspected only when there occurs a delay in wound healing or when there are disturbances of gastrointestinal motility. Prolongation of the emptying time of the stomach may be present so that as much as 60 per cent of a barium sulfate meal may be retained six hours after ingestion. Edema of the stoma of a gastroenterostomy may lead to obstructive symptoms. Diminution of the peristalsis of the intestines may occur and, when accompanied by distention of the intestines, may closely simulate adynamic ileus. These patients frequently do not show evidences of general malnutrition. In table 4 are recorded data on a group of patients in whom hypoproteinemia was not accompanied by edema of the subcutaneous tissues. It is significant that in none of these patients were there evidences of infection. It will be noted, too, that fluid intake and output were within normal limits.

The edema which is presented by patients of group 3 renders simple the recognition of the underlying hypoproteinemia. These patients often are poorly nourished. Moreover, hypoproteinemia in this group is generally associated with one or more of the following accessory factors: tissue protein defects due to malnutrition, excessive fluid and salt intake or sepsis.

PHYSIOLOGIC ASPECTS OF THE THERAPEUTIC PROBLEM

The response to therapy of hypoproteinemia will depend to a large extent on the type, whether this is prehepatic, hepatic or posthepatic. The coexistence of a depleted reserve of plasma protein-building material as in the prehepatic type, or severe liver damage, as in the hepatic type, renders hypoproteinemia less responsive to treatment. For this reason, the posthepatic type of hypoproteinemia, e. g., that associated with burns, usually responds rapidly to treatment. The importance of the type of hypoproteinemia from the viewpoint of therapy is illustrated by the following case reports:

CASE 1.—*Hypoproteinemia—prehepatic type.*

J. L., a Negro woman aged 33 years, presented herself at Charity Hospital with a history of increasing constipation. Owing to pain associated with attempts at defecation, there had been a voluntary restriction of diet. Physical examination disclosed an extremely emaciated Negro woman with grade 4 pitting edema of the lower extremities extending to the knees. A rectal stricture which barely admitted the tip of the index finger was present. The serum protein level was 5.17 Gm. per hundred cubic centimeters, and the result of the intravenous hippuric acid test of liver function was 0.204 Gm. (normal, 0.7 Gm.). Despite blood transfusions, the serum protein level dropped to 3.93 Gm. per hundred cubic centimeters, and the edema persisted. Death resulted.

CASE 2.—*Hypoproteinemia—hepatic and posthepatic type.*

J. P., a Negro woman aged 38 years, presented herself at Charity Hospital with evidences of pelvic peritonitis which followed dilation of a rectal stricture with bougies. While she was in the hospital, the temperature ranged between 99 and 103 F. Blood examination showed increasing anemia and leukocytosis (26,500 cells). The patient became jaundiced (the icterus index was 17; the van den Bergh test had a direct delayed reaction). The serum protein level fell to 5.21 Gm. per hundred cubic centimeters. Edema of the lower extremities and the face appeared. The result of the intravenous hippuric acid test of liver function was 0.276 Gm. (normal, 0.7 Gm.). Repeated blood transfusions produced a slow rise in the serum protein level to 6.29 Gm. per hundred cubic centimeters. Coincidentally, the function of the liver improved, as indicated by the intravenous hippuric acid test, the result of which was now 0.798 Gm. The edema diminished greatly, but pitting edema of the ankles (grade 1) persisted until the temperature returned to normal, i. e., two weeks after the return of the serum protein to the normal level.

CASE 3.—*Hypoproteinemia—posthepatic type.*

A. T., a young white man aged 23 years, was severely burned on the arms and the trunk. Edema of the face and the lower extremities appeared on the third day after admission to Charity Hospital. The patient had been receiving 2,500 to

3,000 cc. of 5 per cent dextrose in physiologic solution of sodium chloride daily. The serum protein level was 4.6 Gm. per hundred cubic centimeters at this time. One transfusion of 350 cc. of ascitic fluid was given. Marked diuresis occurred. The following day the edema had disappeared, and the serum protein level had risen to 6.8 Gm. per hundred cubic centimeters. The excellent response to treatment in this patient was due to the fact that no depletion of the tissue proteins or of the protein reserve in the liver had occurred.

Edema, as well as hypoproteinemia, varies in its response to treatment. Edema which follows the administration of fluids to patients with hypoproteinemia appears to be more responsive to treatment than that which occurs spontaneously during the development of hypoproteinemia. Since the function of the liver is frequently lowered in all types of hypoproteinemia, a diet designed to protect the liver should be given. A high carbohydrate, high protein and low fat diet and the administration of solutions of dextrose by vein will be found useful.

The presence of infection offers a serious barrier to the effective treatment of hypoproteinemia and edema. Infection not only reduces the protein-regenerating ability of the liver, but it also tends to favor the formation of edema by altering the permeability of the capillaries. Hypoproteinemia in the presence of infection should be treated not by plasma, serum or ascitic fluid but by fresh whole blood, which helps the patient to combat not only hypoproteinemia but also infection.

Localized collections of pus should be opened and drained as soon as possible. The local and general use of chemotherapeutic agents, such as sulfanilamide and its derivatives is not contraindicated in infections associated with hypoproteinemia. We have used these drugs successfully in patients with hypoproteinemia. Nevertheless, caution should be exercised, since hypoproteinemia is often associated with a diminution of hepatic function and since sulfanilamide and its derivatives can exert a deleterious effect on the liver.⁴⁹

Hypoproteinemia may be complicated by the presence of a deficiency of vitamins B₁ and C. In certain patients it is difficult to distinguish the edema of hypoproteinemia from that of beriberi. The addition of these vitamins to the diet may produce a more rapid response of hypoproteinemia to treatment.

Not infrequently patients with hypoproteinemia will exhibit evidences of severe secondary anemia, particularly if there is coexistent infection. If edema is present in such patients, it will disappear when adequate measures are taken to relieve hypoproteinemia and infection. In a small group of patients, however, edema persists until anemia is cured. This phenomenon has been observed by Salah²⁸ in the helminthic types of anemia.

49. Davis, H. A.; Harris, L. C., and Schmeisser, H. C.: The Toxic Effects of Sulfanilamide upon Tissues of Rats, *J. Lab. & Clin. Med.* **25**:1263-1275 (Sept.) 1940.

Since operative intervention is frequently necessary, the use of anesthesia in patients with hypoproteinemia must be discussed. It has been conclusively demonstrated by many workers that both general and spinal anesthesia affect liver function adversely. Since the function of the liver is usually diminished in hypoproteinemic states, general and spinal anesthesia carry an increased hazard. Thus, it has been shown that preliminary damage of the liver by chloroform renders animals susceptible to "hypoproteinemic" shock produced by plasmapheresis.³⁹ The conclusion is obvious that every effort must be made to rectify hypoproteinemia and to restore the functional ability of the liver in operative patients before subjecting them to either general or spinal anesthesia.

The factors affecting the response of the patient with hypoproteinemia to treatment can now be summarized as follows:

Favorable Factors:

1. Amenability of the underlying causative condition to treatment.
2. Normal liver function or, alternatively, reduction of liver function due to hypoproteinemia alone.
3. Short duration of hypoproteinemia, since this would indicate the probable existence of reserves of whole proteins and precursors of protein in the liver.
4. Absence of tissue protein defect.
5. Absence of subcutaneous edema or, if present, short duration of subcutaneous edema.

Unfavorable Factors:

1. Lack of amenability of the underlying causative condition to treatment.
2. Reduction of liver function due to causes other than hypoproteinemia itself.
3. Prolonged duration of the hypoproteinemic state prior to treatment.
4. Presence of tissue protein defect.
5. Presence of subcutaneous edema, especially if this is prolonged.
6. Presence of infection.
7. Presence of accessory nutritional deficiency, e. g., beriberi, pellagra.

A paradoxical problem from the viewpoint of therapy is presented by the concurrence of edema and dehydration in patients with hypoproteinemia, in whom attempts to relieve the dehydration result in an increase of the edema. In such patients, treatment should be directed toward hypoproteinemia rather than toward either dehydration or edema, which can be temporarily neglected. The transfusion of plasma, serum or ascitic fluid increases the osmotic pressure of the blood, and fluid is withdrawn from the edematous areas into the blood stream and distributed more equally to the other body tissues.

PROTEIN REPLACEMENT BY THE PARENTERAL ROUTE

The principles underlying the dietary treatment of hypoproteinemia have already been discussed. However, in most patients it is necessary to administer additional proteins or amino acids by the parenteral route.

The forms of protein and amino acids which are available for parenteral use are: (1) whole blood; (2) blood plasma (whole or lyophilized); (3) blood serum (whole or lyophilized); (4) ascitic fluid; (5) digests of casein.

The effects of serum transfusion in nutritional edema in dogs have been studied.⁵⁰ It was found that no significant changes in the amount of edema occurred, despite a definite elevation in the total amount of albumin and globulin in the blood. There was an increase in the blood volume after serum transfusion. This increase was greater than the amount of serum transfused, and Weech and co-workers therefore suggested that water passed from the interstitial tissue spaces into the blood. It is significant that despite the augmentation of the serum proteins, no change in edema occurred.

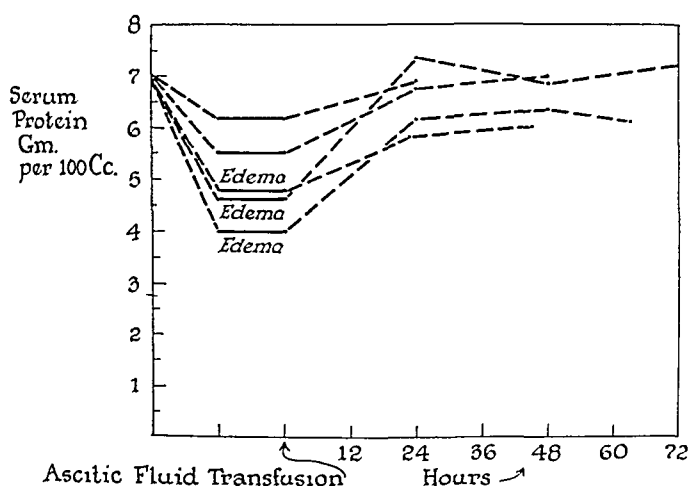


Chart 2.—Effect of the transfusion of ascitic fluid in patients with hypoproteinemia.

Ascitic fluid may be administered either intravenously or subcutaneously in states of hypoproteinemia. The results in several patients are illustrated in chart 2. Ascitic fluid may be administered without preliminary typing or cross matching.⁵¹ The methods of collection and storage of this fluid have been described previously.⁵² Digests of

50. Weech, A. A.; Goettsch, E., and Reeves, E. B.: The Effect of Serum Transfusion on the Plasma Protein Depletion Associated with Nutritional Edema in Dogs, *J. Clin. Investigation* **12**:217-227 (Jan.) 1933.

51. Davis, H. A.: The Inactivation of Group-Specific Isoagglutinins in Relation to the Transfusion of Incompatible Plasma, Serum and Ascitic Fluid, *Surgery* **10**:592-603 (Oct.) 1941.

52. Davis, H. A., and White, C. S.: Human Ascitic Fluid as a Blood Substitute in Experimental Secondary Shock, *Proc. Soc. Exper. Biol. & Med.* **38**:462-465 (May) 1938. Davis, H. A., and Blalock, J. F.: Autologous and Homologous Transfusion of Human Ascitic Fluid, *J. Clin. Investigation* **18**:219-224 (March) 1939.

casein have been used successfully to maintain nitrogen equilibrium when administered by vein⁵³ and subcutaneously.⁵⁴ Recently it was shown that papain digests of casein given intravenously or subcutaneously stimulate new plasma protein production as effectively as protein given by mouth.⁵⁵ It must be remembered, however, that the administration of amino acids, as various groups of workers have suggested, will be effective only if the liver is capable of protein synthesis.

Vitamin C should be administered with such mixtures of amino acids, since recent work⁵⁶ appears to indicate that this vitamin is essential for the proper metabolism of certain amino acids, namely, phenylalanine and tyrosine.

The treatment of edema associated with nephrosis by the intravenous injection of solutions of acacia has been suggested.⁵⁷ However, it has been demonstrated that the injection of acacia interferes with protein regeneration by the liver.⁵⁸

CONCLUSIONS AND SUMMARY

A new classification of hypoproteinemia as prehepatic, hepatic and posthepatic is proposed. The causation of hypoproteinemia and the physiologic and pathologic effects of hypoproteinemia are discussed. The relation of the serum protein level to the function of the liver is considered. It is pointed out that these different forms of hypoproteinemia vary in their responses to treatment. The results of the transfusion of ascitic fluid in hypoproteinemia are reviewed.

53. Elman, R.: Parenteral Replacement of Protein with the Amino-Acids of Hydrolyzed Casein, *Ann. Surg.* **112**:594-602 (Oct.) 1940.
 54. Altshuler, S. S.; Hensel, H. M., and Sahyun, M.: Maintenance of Nitrogen Equilibrium by Amino Acids Administered Parenterally, *Am. J. M. Sc.* **200**:239-244 (Aug.) 1940.
 55. Madden, S. C.; Zeldis, L. J.; Hengerer, A. D.; Miller, L. L., and Whipple, G. H.: A Casein Digest by Vein Utilized to Form Blood Plasma Protein, *Science* **93**:330-331 (April 4) 1941.

56. Levine, S. Z.; Marples, E., and Gordon, H. H.: A Defect in the Metabolism of Tyrosine and Phenylalanine in Premature Infants: I. Identification in Assay of Intermediary Products, *J. Clin. Investigation* **20**:199-207 (March) 1941. Levine, S. Z.; Gordon, H. H., and Marples, E.: A Defect in the Metabolism of Tyrosine and Phenylalanine in Premature Infants: II. Spontaneous Occurrence and Eradication by Vitamin C, *ibid.* **20**:209-219 (March) 1941.
 57. Hartmann, A. F.; Senn, M. J. E.; Nelson, M. V., and Perley, A. M.: The Use of Acacia in the Treatment of Edema, *J. A. M. A.* **100**:251-254 (Jan. 28) 1933.
 58. Andersch, M., and Gibson, R. B.: Studies on Effects of Intravenous Injections of Colloids: Deposition of Acacia in Liver and Other Organs and Its Excretion in Urine and Bile, *J. Pharmacol. & Exper. Therap.* **52**:390-407 (Dec.) 1934.

CHANGES IN THE BLOOD AND THE COMPOSITION OF THE PERITONEAL EXUDATE IN INDUCED SPREADING PERITONITIS

A PRELIMINARY REPORT

J. O. BOWER, M.D.

L. A. TERZIAN, Sc.D.

AND

A. E. PEARCE, M.D.

PHILADELPHIA

Death from appendicitis-peritonitis is one of the major problems of medicine and surgery today, and the condition ranks ninth among the principal causes of death. Appendicitis-peritonitis is the cause of over 92 per cent of so-called deaths from appendicitis, and the mortality rate throughout the United States is approximately 33 per cent. The results of a workable proved plan for reduction of the mortality rate have been published elsewhere.¹

A study of appendicitis-peritonitis induced in the dog, investigations of blood and other body fluids in our own patients and a study of the reaction of 10,306 patients to appendicitis-peritonitis (26 per cent of 39,087 patients with acute appendicitis admitted to 181 hospitals in Pennsylvania over a period of ten years) together indicate that several factors, namely, leukocytosis, the cementing together of loops of intestine by plastic exudate, the migration of the omentum and the presence or absence of antibodies, are responsible for recovery or death of both man and dog.

Delay in hospitalization and the administration of laxatives in an attack of appendicitis are causes of appendicitis-peritonitis, and in man with this disease and in the dog suffering from experimentally induced spreading peritonitis, death results from similar causes. Body fluid changes occurring in both man and dog with appendicitis-peritonitis are important not only from the standpoint of the management of the disease

From the Foundation for Clinical and Surgical Research and the Division of Biochemistry of the Laboratories of the Philadelphia General Hospital.

1. Bower, J. O.: Spreading Peritonitis Complicating Acute Perforative Appendicitis: Routine Operations Versus Scientific Management, *J. A. M. A.* **112**:11-17 (Jan. 7) 1939; Report of the First State-Wide Survey of Acute Appendicitis Mortality, *Pennsylvania M. J.* **43**:1145-1174 (May) 1940.

but also because they reveal other changes which indicate to some degree how defensive mechanisms operate.

Comparative analyses of the peritoneal exudate obtained from human patients with peritonitis and from dogs with experimental peritonitis shown in table 1 suggest that similar pathologic and physiologic reactions have taken place. The data presented in table 1 indicate that the fluid obtained from the peritoneal cavity of these subjects contains large amounts of plasma protein. As will be shown later, in the experiments

TABLE 1.—*Comparison of the Constituents of Blood and Peritoneal Exudate of Man and of Dog**

Subject	Pathologic Condition		Hemato- crit Value	Total Protein	Albu- min	Albumin Globulin Ratio	Chloride
A. Man							
B. D.	Acute catarrhal appendicitis	Blood	7.5	5.2	2.2	. .
		Peritoneal exudate	5.7	4.1	2.5	. .
E. K.	Appendix gangrenous, serous coat intact	Blood	7.0	4.5	1.8	575
		Peritoneal exudate	6.3	4.5	2.3	545
V. K.	Spreading peritonitis, perforated duodenal ulcer	Blood	47.5	6.6	3.7	1.3	695
		Peritoneal exudate	3.8	2.4	1.7	645
B. Dog							
39	Appendix gangrenous, localizing process	Blood	7.1	4.1	1.4	670
		Peritoneal exudate	6.2	3.8	1.6	655
93	Appendix gangrenous, localizing process	Blood	7.7	4.2	1.2	620
		Peritoneal exudate	7.0	4.2	1.5	620

* This table shows not only the close approximation of the protein content of the blood and the peritoneal exudate in man and dog but also an increase in these with each advanced step of the disease (compare analysis of dog 39 with first analysis in table 2). An exception to this was the peritoneal exudate associated with perforated duodenal ulcer; in this case the quantity of fluid was excessive and probably accounted for the comparatively low protein content of both blood and peritoneal exudate. The localizing process referred to is an early perforation of a gangrenous appendix in the process of being walled off from the general peritoneal cavity by loops of intestine and omentum cemented together with plastic exudate. Free in the general peritoneal cavity in both man and dog will be found a varying amount of bacteria-free peritoneal exudate.

described in this paper, these changes have an important relation to the course of the infection.

EXPERIMENTAL METHODS

Adult mongrel dogs weighing an average of 16 Kg. and in a good nutritional state were used. In every instance control blood examinations were made prior to the experimental production of peritonitis.

Laboratory Methods.—(a) Plasma volume and blood volume were estimated according to a modification of the method outlined by Gibson and Evans,² using the dye T 1824. Blood samples were taken either by vein or by cardiac puncture, and the concentration of the dye was estimated by means of a Summerson photo-

2. Gibson, J. G., Jr., and Evans, W. A., Jr.: Clinical Studies of Blood Volume: Changes in Blood Volume, Venous Pressure and Blood Velocity Rate in Chronic Congestive Heart Failure, *J. Clin. Investigation* 16:851-858 (Nov.) 1937.

electric colorimeter. It was found that error due to hemolysis or lactescence could be overcome by treating the plasma with acetone. Dye concentrations were measured in the clear fluid remaining after centrifugation. Details will be reported in a separate paper.

(b) Determinations of total protein and albumin were made according to the methods described by Kingsley,³ globulin being calculated by difference. Total circulating protein was calculated from plasma volume and grams of protein per cubic centimeter. As will be reported elsewhere, in some few cases there were certain differences between biuret protein and protein as determined by the Kjeldahl method. These differences, however, were not of sufficient magnitude to affect the results in this series of experiments.

(c) Determinations of hemoglobin were done by the method of Sanford, Sheard and Osterberg.⁴ For determination of red blood cell volume, Sanford-Magath hematocrit tubes were used, and the sample was centrifuged at 3,000 revolutions per minute for thirty minutes. Heparin was used as an anticoagulant.

(d) Chloride was determined by the method of Van Slyke.

Operative Technic.—Prior to operation small doses of morphine and atropine were administered subcutaneously. Anesthesia induced with ether and aseptic technic were employed.

Spreading peritonitis was induced according to the procedure described by Bower, Burns and Mengle.⁵ The appendix and its mesentery, together with all its blood vessels, were ligated, and the appendix was traumatized. In one series, 60 to 90 cc. of castor oil, varied according to the weight of the animal, was administered by catheter immediately after operation.

Management.—During the first series of experiments water was usually given to the animals twelve or fourteen hours after operation, but because persistent vomiting occurred, especially in those dogs given castor oil, water was subsequently withheld for forty-eight hours from dogs treated with castor oil, and for at least twenty-four hours from dogs not receiving castor oil.

EXPERIMENTAL OBSERVATIONS

Series 1 (Ligation of the appendix and its mesentery and administration of castor oil).—Table 2 presents data obtained from the first series of animals in which the appendix and its mesentery were ligated and castor oil was administered. In each case within twenty-four to forty-eight hours after operation, during which time spreading peritonitis developed, there was considerable rise in the total protein and albumin, accompanied by a rise in the hematocrit value. Considerable depletion of chloride occurred. This was most marked in the animals that vomited.

3. Kingsley, G. R.: The Determination of Serum Total Protein, Albumin and Globulin by the Biuret Reaction, *J. Biol. Chem.* **131**:197-200 (Nov.) 1939; A Rapid Method for the Separation of Serum Albumin and Globulin, *ibid.* **133**:731-735 (May) 1940.

4. Sanford, A. H.; Sheard, C., and Osterberg, A. E.: Photometer and Its Use in the Clinical Laboratory, *Am. J. Clin. Path.* **3**:405-420 (Nov.) 1933.

5. Bower, J. O.; Burns, J. C., and Mengle, H. A.: Spreading Peritonitis Complicating Acute Perforative Appendicitis, *Arch. Surg.* **37**:751-759 (Nov.) 1938.

The initial increase in concentration of plasma protein and red blood cells was followed by anemia and hypoproteinemia. The initial increase in protein and red blood cell concentration suggested considerable dehydration accompanied by hemoconcentration, and, in spite of apparently rising protein values, a probable loss of plasma proteins. Although it was obvious from these data that fluid loss had taken place, it was impossible to measure the actual severity of the losses from these determinations alone. For this reason blood volume studies were undertaken.

Blood volume determinations were made twenty-four and forty-eight hours after operation and at various intervals thereafter until the plasma

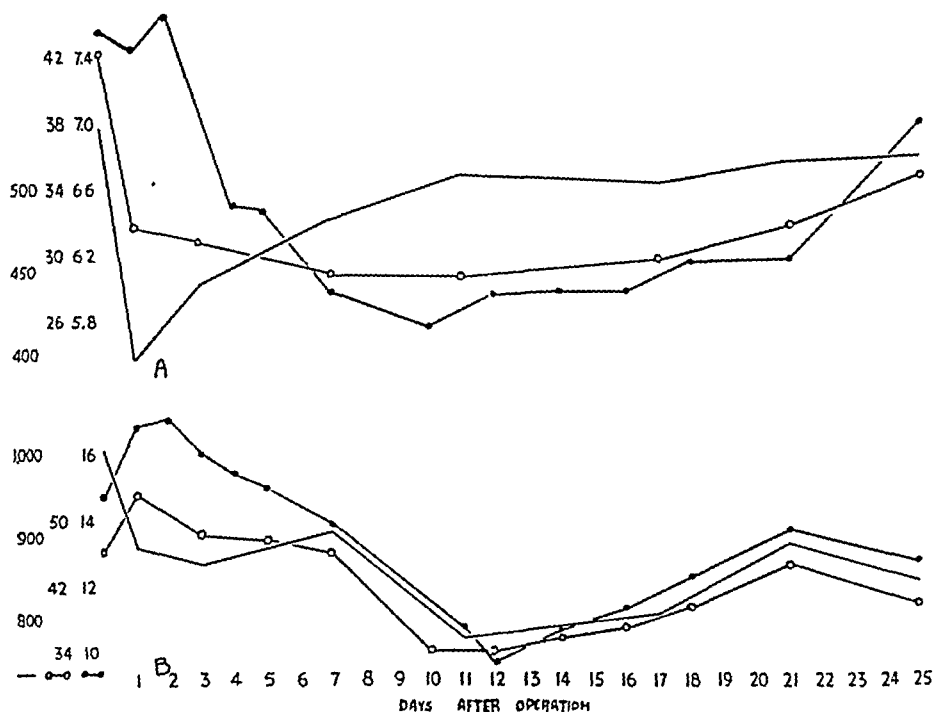


Chart 1 (dog 24).—Chart showing the effects of ligation of the appendix and its mesentery with postoperative administration of castor oil: *A*, changes in protein and in plasma volume over a period of twenty-five days following experimentally induced peritonitis; *B*, changes in hemoglobin, hematocrit value and blood volume over the same period. In *A*, the black line represents the plasma volume (cubic centimeters); the line with the open circles, the total circulating plasma protein (grams); the line with the black dots, the protein per hundred cubic centimeters of plasma (grams). In *B*, the black line represents the blood volume (cubic centimeters); the line with the open circles, the per cent red blood cell volume; the line with the black dots, the hemoglobin per hundred cubic centimeters of blood (grams).

volume had returned to normal or nearly normal values. The resulting changes following operation in total circulating protein, plasma volume and per cent red blood cell volume are presented in chart 1 and table 2. In each dog within twenty-four to forty-eight hours after operation, there

was considerable fall in plasma volume, a decrease in the amount of circulating protein, and, concurrent with the plasma losses, an increase in concentration of the cellular elements of the blood as evidenced by the

TABLE 2.—Blood Changes During the Course of Experimental Peritonitis Induced by Ligation of the Appendix with Postoperative Administration of Castor Oil

Dog		Normal	Days After Operation										Plasma Loss, %	Protein Loss, %
			1	2	3	4	5	6	7	8	9	10		
3	Total protein.....	7.3	8.05	7.8	6.5	6.5	6.3	6.3	6.0	6.0	5.9	6.2
	Hematocrit value...	46.5	53.4	47.8	45.0	42.4	37.0	33.2	32.5	30.0	28.8	34.0
	Chloride.....	670	670	670*	595	570	550	605	645	...	650
4	Total protein.....	5.7	6.5	7.1	6.2	6.2	5.6	5.4	5.2	5.2	5.2	5.3
	Hematocrit value...	46.0	48.5	47.5	43.2	43.1	41.5	37.3	37.2	36.1	35.6	35.0
	Chloride.....	650	650	655*	585*	600	585	640	635
5	Total protein.....	6.2	7.2	7.8	7.5	Died								
	Hematocrit value...	49.0	61.2	61.4	61.4									
	Chloride.....	675	655	675*	505									
9	Total protein.....	6.0	6.7	Died										
	Hematocrit value...	48.8	64.2											
	Chloride.....	675	610*											
10	Total protein.....	6.0	6.8	6.0	5.8	5.6	4.8	5.2	5.4	6.0
	Hematocrit value...	50.2	61.3	60.2	52.1	50.1	43.0	41.0	42.0	42.5
	Chloride.....	650	650*	565	545	550	630	670	665
18	Total protein.....	6.0	7.7	Died										
	Hematocrit value...	56.0	69.0											
	Chloride.....	655	645											
19	Total protein.....	5.4	6.3	7.0	Died									
	Hematocrit value...	42.5	50.3	46.5										
	Chloride.....	655	630	605										
16	Plasma volume.....	500	...	395	...	415	445	21.0
	Total circulating protein.....	29.5	...	25.6	...	26.9	25.8	13.5
	Hematocrit value...	45.0	52.5	50.0	46.0	46.0	...	45.0	40.5
	Chloride.....	635	620	595	630	640	...	590	615
17	Plasma volume.....	540	405	...	495	560	25.0
	Total circulating protein.....	31.8	27.0	...	30.6	32.3	12.2
	Hematocrit value...	46.0	50.0	55.1	52.3	48.2	...	46.4	37.0
	Chloride.....	645	645*	635	590	605	...	595	560
20	Plasma volume.....	825	720	Died		12.5
	Total circulating protein.....	48.0	44.0	8.5
	Hematocrit value...	48.5	56.5
	Chloride.....	640	640
23	Plasma volume.....	685	...	525	Died		23.2
	Total circulating protein.....	42.5	...	35.7	16.0
	Hematocrit value...	50.9	58.0	57.7	59.0
	Chloride.....	640	640*	655	670*
24	Plasma volume.....	540	405	...	445	450	26.0
	Total circulating protein.....	42.6	32.0	31.1	29.2	25.0
	Hematocrit value...	46.0	53.5	53.3	49.0	49.5	48.5	...	46.7
	Chloride.....	650	645	640	600	540	530	...	570
Average.....												21.5	14.9	

* Vomiting occurred.

rise in hematocrit value and in hemoglobin. Since the hematocrit value was found to parallel the hemoglobin concentration, the latter is not included in the table or the chart. In addition there was considerable

depletion of plasma chloride unrelated to vomiting, although losses of chloride were most marked when vomiting occurred. This is shown by the decrease which took place in dog 24.

Reference to table 2 will show that there was considerable variation in the extent of the loss of plasma and protein and in the individual reactions of the animals to the infection. In this series no relation could be shown between the extent of the loss of protein and plasma and the probable recovery or death of the animal. For example, dog 20 suffered a loss in plasma volume of 12.5 per cent and a loss of protein of only 8.5 per cent, yet it failed to survive. Dog 23 showed losses of 23.2 per cent and 16.0 per cent, and it, too, failed to survive. On the other hand, dog 24, which showed much greater losses in protein but a somewhat lesser loss in plasma volume, recovered in time, and dogs 16 and 17, which showed much greater changes than dog 20, also recovered. Although considerable losses in plasma and protein occur during the course of spreading peritonitis and although the degree of these losses determine to some extent the survival of the animals, in this particular series it seems that other factors, viz., leukocytosis and omental migration, also played a significant part.

Chart 1 shows in greater detail the changes taking place over an extended period in dog 24. The significant features are the drop in plasma volume and in the total circulating protein twenty-four hours after operation. In this particular animal, the plasma volume dropped from a normal value of 540 to 405 cc., while the total circulating protein dropped from 42.6 to 32.0 Gm. Two other features are to be noted: (1) the lengthy period of hypoproteinemia, indicating that once protein reserves have been seriously depleted, resynthesis of sufficient protein with recovery to the normal level is attended with considerable difficulty and (2) the extended period of time required by the animal to reestablish normal plasma volume. As plasma volume is restored, red blood cell formation fails to keep pace, and anemia becomes apparent and persists over a considerable period. In almost all cases the period of convalescence is characterized by long-standing anemia. It is of interest to note also that protein levels alone constitute an inaccurate index of the actual quantity of circulating protein and that it is only when plasma volume has been reestablished to some extent that the concentration of plasma protein approximates a true indication of the amount of protein present.

Chart 1 *B* represents the changes in hemoglobin, per cent red blood cell volume and total blood volume. The changes in this case parallel the changes demonstrated in chart 1 *A*. Coincident with the loss of plasma there was an increased concentration of the cellular elements and the hemoglobin, while the blood volume itself decreased 11.3 per cent in twenty-four hours.

Series 2 (Ligation of the appendix and its mesentery with no administration of castor oil).—Data for the series of animals in which the appendix and its mesentery were ligated and castor oil was not administered.

TABLE 3.—Blood Changes During the Course of Experimental Peritonitis Induced by Ligation of the Appendix Without Postoperative Administration of Castor Oil

Dog		Normal	Days After Operation							Plasma Loss, %	Protein Loss, %
			1	2	3	4	5	6	7		
25	Total protein.....	7.5	7.5	8.35	Died						
	Hematocrit value....	35.0	40.5	49.3							
	Chloride.....	620	610	620							
26	Total protein.....	6.6	6.8	Died							
	Hematocrit value....	52.0	62.8								
	Chloride.....	635	610								
27	Total protein.....	6.2	6.5	Died							
	Hematocrit value....	42.2	48.8								
	Chloride.....	620	...								
31	Total protein.....	6.3	6.6	Died							
	Hematocrit value....	44.6	57.2								
	Chloride.....	610	...								
32	Total protein.....	6.2	6.5	7.1	Died						
	Hematocrit value....	52.3	59.4	71.4							
	Chloride.....	615	640	...							
21	Plasma volume.....	710	550	...	595	...	685	22.5	...
	Total circulating protein.....	42.6	31.5	...	32.0	...	37.0
	Hematocrit value....	51.8	61.3	56.2	52.5	51.6	43.6	19.0
	Chloride.....	645	645	670	650	660	610	...	42.3
22	Plasma volume.....	545	...	415	...	510
	Total circulating protein.....	33.8	...	28.2
	Hematocrit value....	50.0	51.3	55.6	51.6	35.0	23.9	...
	Chloride.....	630	615	615	605	51.0	16.3
28	Plasma volume.....	580	415	...	430	560
	Total circulating protein.....	42.3	32.0
	Hematocrit value....	50.0	54.2	56.9	52.5	50.2	28.5	...
	Chloride.....	610	...	615	...	605
29	Plasma volume.....	685	420	Died	30.2
	Total circulating protein.....	44.5	31.0	40.3	37.1	...	25.5
	Hematocrit value....	49.8	58.3	635
	Chloride.....	630	...	61.2	38.7	...
30	Plasma volume.....	545	...	385	30.5
	Total circulating protein.....	33.8	...	28.5	...	410	Died
	Hematocrit value....	45.5	53.0	58.0	54.5	29.0	20.5	...
	Chloride.....	645	...	645	...	51.5
35	Plasma volume.....	880	...	695	...	915	15.6
	Total circulating protein.....	52.0	...	43.2
	Hematocrit value....	46.0	46.0	48.2	41.0	48.5	915	21.0	...
	Chloride.....	645	640	640	...	610	50.3	...	17.2
37	Plasma volume.....	945	710	...	775	650
	Total circulating protein.....	59.6	46.5	...	42.6	775	25.0	...
	Hematocrit value....	48.8	55.2	...	45.6
	Chloride.....	665	615	620	...	41.6	44.2	...	20.2
Average.....			36.6
									650	27.0	20.6

istered are presented in table 3. The changes parallel those which occurred in the animals given castor oil except that in this particular series the plasma volume and total circulating protein losses were some-

what greater—average losses of 27.0 and 20.6 per cent, respectively, as compared with 21.5 and 14.9 per cent in the animals given castor oil. There was considerable variation in the size of the appendix in different animals, and it is possible that dogs with comparatively larger ceca were more severely traumatized by the operation and as a consequence suffered a more severe reaction. Further, the amount of manipulation necessary to deliver the organ was undoubtedly responsible in some degree for the extent of reaction in the animal. However, both series were too small to enable one to draw any positive conclusions, and with so many factors involved it would be difficult to ascribe the degree of the changes to any one particular cause.

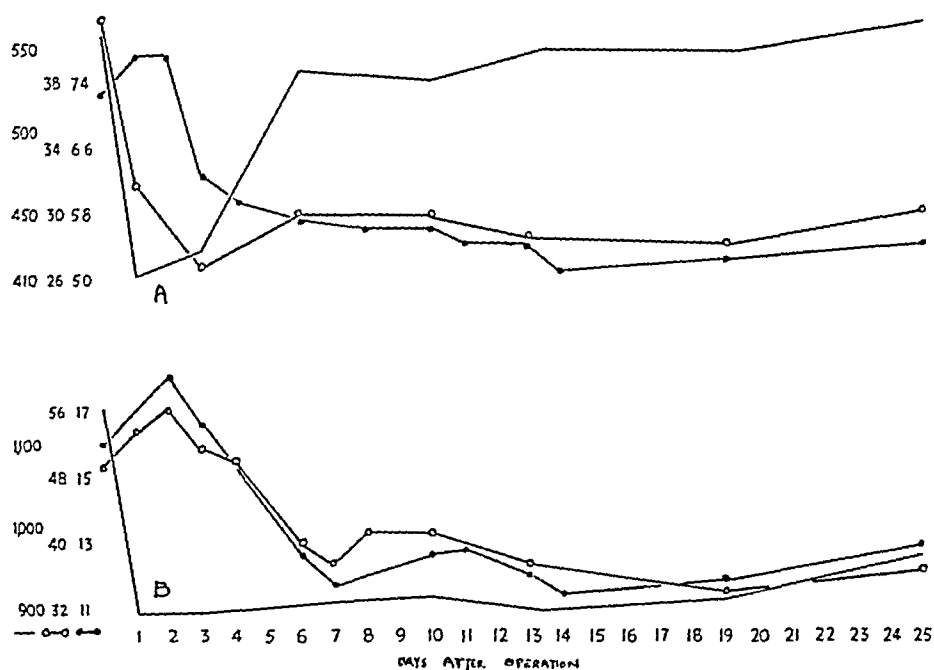


Chart 2 (dog 28).—Chart showing the effect of ligation of the appendix and its mesentery without the postoperative administration of castor oil: *A*, changes in protein and in plasma volume over a period of twenty-five days following experimentally induced peritonitis; *B*, changes in hemoglobin, hematocrit value and blood volume over the same period of time. In *A*, the black line represents the plasma volume (cubic centimeters); the line with the open circles, the total circulating plasma protein (grams); the line with the black dots, the protein per hundred cubic centimeters of plasma (grams). In *B*, the black line represents the blood volume (cubic centimeters); the line with the open circles, the per cent red blood cell volume; the line with the black dots, the hemoglobin per hundred cubic centimeters of blood (grams).

There is, nevertheless, one difference between this group and the group given castor oil; animals not given castor oil that survived were able to restore the plasma volume to normal levels within a comparatively

shorter period. Animals not given castor oil are usually able to retain fluids twenty-four hours after operation, while animals which have received castor oil vomit persistently for several days thereafter, thereby precluding the possibility of any appreciable amount of fluid intake by mouth. This may explain in part why restoration of plasma volume is more rapid in animals not given castor oil. Dog 37 constitutes a notable exception in that it failed to recover its normal plasma volume. The probable explanation may lie in the fact that this animal suffered persistent diarrhea from the fifth day on and finally had to be discarded for that reason. Graphic representation of the course of dog 28 in chart 2, which was typical of the group as a whole, brings out these features more clearly. Twenty-four hours after operation there was a

TABLE 4.—*Blood Studies of Animals Killed at Various Intervals After Ligation of the Appendix and the Production of Peritonitis*

Dog	Hematocrit Value	HbO ₂	Total Protein	Albumin	Albumin-Globulin Ratio	Chloride	Carbon Dioxide	Plasma Volume	Total Circulating Protein
39 Normal.....	44.0	11.9	6.0	3.9	1.8	670	38	780	46.8
24 hr. after operation.....	63.5	17.9	7.1	4.1	1.4	670	36	520	36.9
Peritoneal fluid..	6.2	3.8	1.6	655	29
42 Normal.....	55.0	16.9	7.0	3.7	1.1	645	..	685	48.0
48 hr. after operation.....	66.1	21.0	7.9	3.6	0.86	615	..	530	41.8
Peritoneal fluid..	6.5	3.5	1.1	650
43 Normal.....	45.0	14.5	7.1	4.0	1.3	635	36	660
24 hr. after operation.....	53.5	16.4	7.7	4.2	1.2	620	35	560
Peritoneal fluid..	7.0	4.2	1.5	620	24

28.5 per cent loss in plasma volume, with an attendant decrease of 25.5 per cent in total circulating protein. However, in this case, the animal was able to restore its plasma volume to almost normal levels within six to seven days. As a consequence of the more rapid restoration of plasma volume, the resulting anemia became apparent earlier in the course of the disease and was conspicuous throughout the period of recovery.

*Series 3 (Animals killed at intervals following operation).—*The purpose of the series of experiments in which the animals were killed at intervals after operation was to determine the fate of the fluid lost from the vascular system. After ligation of the appendix without post-operative administration of castor oil, dogs were killed at various intervals. Blood samples were taken, blood volume determinations were made, and the animals were killed and immediately subjected to autopsy. The results of these studies are summarized in table 4. All the animals showed acute spreading peritonitis. Gross perforation had occurred in

dog 42, but fecal material was present only in a localized area around the lesion which already had been walled off and sealed in to some extent by loops of the intestine. In each case there was present in the peritoneal cavity a considerable amount of serosanguineous fluid which was sponged out and measured. Centrifugation of this yielded a clear plasma-like supernatant fluid. Analysis yielded the result shown in table 4, indicating that the major part of the fluid and protein losses from the vascular system could be accounted for by the fluid present in the peritoneal cavity. One would expect the smaller-sized albumin molecules

TABLE 5.—*Blood Changes in Normal Dogs Following Laparotomy*

Dog		Normal	Days After Operation							Plasma Loss, %	Protein Loss, %
			1	2	3	4	5	6	7		
33	Plasma volume	700	...	700	730	...	780	11.5	...
	Total circulating protein.....	51.0	...	46.3	48.8	...	53.0	...	9.0
	Hematocrit value ..	40.3	46.5	44.7	11.5	39.2	38.8	...	39.6
	Chloride.....	640	635	635	635	650	650	...	650
34	Plasma volume.....	745	720	...	685	...	710	...	730	3.5	...
	Total circulating protein.....	42.5	41.2	...	39.5	...	40.4	...	42.8	...	3.3
	Hematocrit value ..	39.6	40.0	40.5	38.0	37.5	38.0	...	38.0
	Chloride.....	635	620	635	635	635	650	...	635
26	Plasma volume.....	830	...	785	..	785	850	6.5	...
	Total circulating protein.....	58.2	...	53.5	...	52.0	56.5	...	8.0
	Hematocrit value ..	42.5	16.2	46.0	43.0	45.7	45.0	...	43.0
	Chloride.....	615	640	635	...	615	635
35	Plasma volume....	775	755	...	735	735	3.6	...
	Total circulating protein.....	44.5	43.0	...	41.8	41.2	...	3.3
	Hematocrit value ..	33.0	53.0	55.2	33.0	46.5	45.0	...	44.2
	Chloride. . .	665	640	640	640	635	650
Average.....										6.0	5.9

to leak out more quickly than the globulin, and this is borne out by the fact that the albumin-globulin ratio of the peritoneal fluid was higher than that of the plasma with corresponding lowering of the normal plasma ratio.

Series 4 (control series).—To rule out the effects of operation alone, laparotomies were performed on a group of animals under conditions as nearly identical to the original operations as possible except, of course, that the appendix was not ligated. In each case the animals were prepared for operation as described and held under ether anesthesia; the viscera were manipulated in the manner required for the actual operation. The results in this series of animals are presented in table 5. All animals survived the operation. Although there were losses in plasma volume and circulating proteins averaging 5.9 and 6.0 per cent.

respectively, in twenty-four to forty-eight hours, the magnitude of the changes is not comparable to the extensive losses taking place in experimentally induced peritonitis. Further, with the exception of dog 38, in which a draining abscess developed at the site of incision, all the animals were able to recover their plasma volume and protein losses within five or six days.

As an additional control, water was withheld from 1 animal for a period of forty-eight hours, during which time volume studies were done. The loss in plasma volume at the end of forty-eight hours due to dehydration amounted to 5.5 per cent of the normal volume, indicating that although deprivation of water in the postoperative management of the animals is an additional factor responsible for changes in blood volume, such treatment alone cannot account for the marked changes which take place during the course of peritonitis.

COMMENT

The results reported in this paper indicate that there are produced in experimental peritonitis profound changes in the quantity and the distribution of body fluid. There is a decrease in plasma volume, a decided loss of circulating plasma proteins, an increase in the concentration of the cellular elements and a loss of plasma electrolytes. These changes resemble those preceding or accompanying shock, resulting from extensive operations, severe injuries and infections. The operation itself and the traumatization of the cecum are undoubtedly factors contributing to the fluid losses, but the induced spreading peritonitis appears to be the factor mainly responsible for the radical changes which take place and which result in the serious alterations in the blood. It is not the purpose of this paper to inquire as to the probable mechanisms responsible for producing the conditions of shock but rather to emphasize the fact that there are associated with spreading peritonitis changes similar to those of shock.

Although the systemic reactions of these animals were of varying degrees of severity, they were in general similar to those reported by Evans,⁶ who produced shock in dogs by strangulating a short loop of the terminal ileum. Here again, as in traumatic shock, plasma loss appears to be local.⁷

There has been considerable criticism of the dye method for estimating blood volume on the grounds that during the conditions of shock the dye rapidly diffuses out of the blood system, thereby producing serious errors

6. Evans, E. I.: The Mechanism of Shock in Intestinal Strangulation, *Am. J. Physiol.* **133**:P271 (June) 1941.

7. Blalock, A.: Principles of Surgical Care, Shock and Other Problems, St. Louis, C. V. Mosby Company, 1940. Harkins, H. N.: Recent Advances in the Study and Management of Traumatic Shock, *Surgery* **9**:607-655 (April) 1941.

in results. In the group of animals killed at various intervals after operation, T 1824 was injected intravenously one half to three quarters of an hour prior to autopsy. Colorimetric examination of the centrifuged fluid derived from the peritoneal cavity failed to reveal the presence of dye. This suggests that the capillaries were still selectively impermeable to the dyestuff circulating in the blood system at least with regard to diffusion into the peritoneal cavity.

CONCLUSIONS

Following experimental peritonitis there is a loss of plasma volume and of blood volume with attendant loss of plasma protein and electrolyte.

Fluid present in the peritoneal cavity contains large amounts of plasma protein and accounts for much of the plasma loss.

Dependent on the degree of plasma loss there is an increase in the concentration of the cellular elements of the blood.

The most acute changes occur within twenty-four to seventy-two hours after operation. Following this critical stage of the infection there is an extended period of anemia during convalescence.

Accompanying preperforative appendicitis, appendicitis-peritonitis and spreading peritonitis from other causes in man there are varying amounts of fluid present in the peritoneal cavity containing large amounts of plasma protein and electrolytes.

Drs. J. H. Clark and J. G. Reinhold, of the Philadelphia General Hospital, gave cooperation in this study.

ESOPHAGEAL DIVERTICULA

J. DEWEY BISGARD, M.D.

OMAHA

The relative merits of the one stage and the two stage operation for the cure of esophageal diverticula have been discussed at length by many advocates of both methods. It is mutually agreed that the only deterrent of the one stage operation is the hazard of soiling the fascial spaces with the dire consequences of unlimited infection. The two stage operation

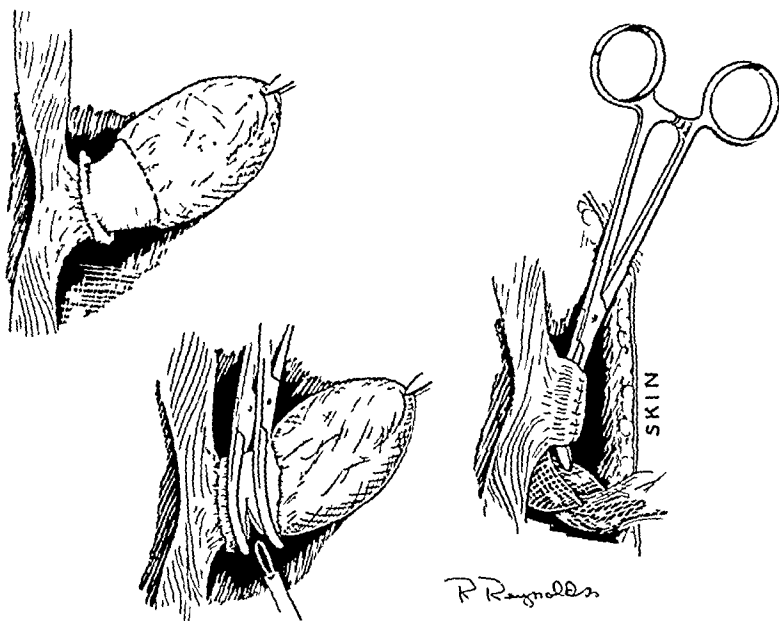


Fig. 1.—The principle of the Maxeiner operation.

permits of walling off these spaces before soiling can occur, and it is the majority surgical opinion that this factor of safety outweighs the disadvantages of the more prolonged and cumbersome procedure.

In 1939, Maxeiner¹ reported an operation performed in one stage which he stated “possesses all of the merits of the two stage operation, most important of which is elimination of wound contamination and infection but which may be accomplished by a single operation.”

In principle, the operation is an aseptic resection accomplished by division of the neck of the diverticulum between hemostats with a

1. Maxeiner, S. R.: The Present Surgical Management of Esophageal Diverticula with Presentation of a New (?) Method, Tr. West. S. A. 49:365, 1939.



Fig. 2 (case 3).—Five days after operation. The hemostat and the Levine tube for direct gastric feedings are still in place.



Fig. 3 (case 3).—*A* and *B*, roentgenograms taken before operation. *C*, roentgenogram taken ten days after operation; *d*, the former site of the diverticulum.

cautery. The proximal hemostat, which seals the wall of the esophagus, remains in place with its handles exteriorized through the wound. By the time the hemostat sloughs off in from six to eight days, walling off of the wound has occurred.

This operation with minor variations has been used by me in 5 cases during the past two years. It is illustrated in figure 1. Because an excellent result was obtained in each instance, this experience is reported as evidence in addition to that reported by Maxeiner and others that the operation is as sound in practice as it is in principle.

The minor variations in technic consisted of placing the occluding hemostat with the handles directed upward and of covering all surfaces of the wound with sulfanilamide powder. In each instance a Levine tube was threaded through a nostril into the stomach immediately after

Data on Five Cases of Esophageal Diverticulum

Case	Age of Patient, Year	Sex of Patient	Duration of Dysphagia	Ingestion of Fluids Only	Loss of Weight, Lbs.	Hemostat Off Days	Duration of Fistula, Days	Post-operative Days in Hospital
1	64	M	1.5 yr.	6 weeks	18 (8.2 Kg.)	7	3	9
2	67	F	7 yr.	1 yr.	30 (13.6 Kg.)	7	2	10
3	76	M	6 mo.	2 mo.	15 (6.8 Kg.)	6	4	12
4	52	M	3 yr.	None	6	3 (recurred)	8
5	51	M	6 yr.	25 (11.3 Kg.)	7	3	8

operation, and high caloric liquids well supplied with proteins and fortified with large doses of vitamin B complex and vitamin C were administered in sufficient quantity to maintain complete fluid balance and to assure normal caloric requirements. This method of feeding was used for five or more days, when food could be swallowed without much difficulty. In 3 cases moderate degrees of malnutrition had developed; the patients were given dextrose and vitamin therapy parenterally for a few days before operation.

Two patients were discharged from the hospital in eight days after operation: 1 was discharged in nine; 1, in ten; and 1 in twelve. In only 1 case did an esophageal fistula persist longer than four days after the hemostat came off and at no time in all cases was there more than a slight seepage. In the 1 case the fistula, which presumably had closed within three days, reopened a few days later through the wound, which had completely healed during the interval. After five days it permanently closed.

Brief reports of cases are given in the table.

INFLUENCE OF VITAMIN B COMPLEX DEFICIENCY AND PARTIAL STARVATION ON WOUND HEALING

EXPERIMENTAL RESEARCH WITH RATS

JANET C. HOLDEN, M.D.

AND

GEORGE CRILE JR., M.D.

CLEVELAND

The literature on the effect of the vitamin B complex on wound healing is confined to observations on surface healing and is summarized by Arey¹ in his article on wound healing. Saitta² found that a deficiency in the vitamin B complex resulted in diminished power of cicatrization in wounds of the skin, the subcutaneous tissue and the muscles. Oral administration of extract of cereals prevented these changes, and direct treatment of the wounds with the vitamin B complex produced normal activation of the cellular repair. Lauber³ emphasized the unreliability of results obtained with the vitamin B complex and attributed this to a lack of standardization of the exact amounts of the vitamin in vitamin B-rich diets. He found no difference in wound healing between control animals and animals fed with yeast. Larcher⁴ found that wounds in pigeons suffering from a deficiency of the vitamin B complex healed with equal rapidity or faster than similar wounds in a control series. Padula⁵ found that the local application of vitamin B complex to a wound slowed the rate of healing in normal animals but increased it in animals maintained on a diet low in vitamins. Healing was found to be still faster when the deficient animals were subsequently given a normal diet to which vitamins were added. Howes, Briggs and Harvey⁶ found that in partially starved adult rats the curve of fibroplasia was not markedly changed from normal.

1. Arey, L. B.: *Physiol. Rev.* **16**:327-406 (July) 1936.

2. Saitta, S.: *Scritti biol.* **5**:273-283, 1930.

3. Lauber, H. J.: *Beitr. z. klin. Chir.* **158**:293-302, 1934.

4. Larcher, A.: *Arch. di fisiol.* **25**:348-360 (July-Sept.) 1927.

5. Padula, A.: *Arch. ital. di chir.* **42**:627, 1936; abstracted, *Internat. Abstr. Surg.* **63**:288, 1936; in *Surg., Gynec. & Obst.*, September 1936.

6. Howes, E. L.; Briggs, H.; Shea, R., and Harvey, S. C.: *Effect of Complete and Partial Starvation on Rate of Fibroplasia in Healing Wound*, *Arch. Surg.* **27**:846 (Nov.) 1933.

EXPERIMENTS TO DETERMINE EFFECT OF A DEFICIENCY OF THE
VITAMIN B COMPLEX ON WOUND HEALING

A series of experiments were carried out on the albino male rat to determine the effect of vitamin B complex deficiency on wound healing.

Two groups of rats were observed; there were 14 rats in each group.

Group 1—Normal adult controls

Group 2—Rats maintained on a diet deficient in the vitamin B complex

Group 1 was given the following normal diet:

Casein	400 Gm.
Osborne-Mendel salt mixture.....	80 Gm.
Corn starch.....	1,320 Gm.
Cottonseed oil.....	160 Gm.
Cod liver oil.....	40 Gm.
Yeast	200 Gm.

Group 2 was given the following diet deficient in vitamin B complex:

Purified casein (heated in an oven at 212 F. for forty-eight hours).....	400 Gm.
Osborne-Mendel salt mixture.....	80 Gm.
Corn starch.....	1,320 Gm.
Cottonseed oil.....	160 Gm.
Cod liver oil.....	40 Gm.

Wound healing in the rats was tested by the method of Harvey.⁷ An experimental wound 2 cm. long was placed in the midline of the wall of the abdomen and was closed with a through and through running suture of black silk. The operation was performed with aseptic technic. The suture was removed one week after operation. The tensile strength of the wound was tested on the eighth and the tenth postoperative day by inflating the abdomen with air injected into the peritoneal cavity through a lumbar puncture needle. The breaking point of the incision was measured on a mercury sphygmomanometer. The appearance of the wound and the presence or absence of peritonitis were noted. The manometer measured only to 300 mm. of mercury, and figures above this level are recorded as 300.

In each group 6 animals were killed on the eighth postoperative day (subdivision A), and 6 animals were killed on the tenth postoperative day (subdivision B).

The seventh animal in each division was used for histologic studies. Each group of rats was kept on its respective diet an equivalent length of time. The rats were weighed once a week. When the vitamin-deficient rats had lost about 30 per cent of their original weight, they were subjected to operation.

The average tensile strength of the wounds was lower in the vitamin B-deficient rats tested on the eighth postoperative day than in the controls, but by the tenth postoperative day the average tensile strength of the wounds of the vitamin B-deficient group was actually a little higher than that of the control group. In this experiment, however, the average tensile strength is perhaps not so significant a figure as the number of rats whose wounds withstood a pressure of 300 mm. of mercury. Since the manometer registered nothing higher than 300, a single low figure, such as the 120 recorded for rat 1 of group 1 A, tends to make a consid-

7. Harvey, S. C.: The Velocity of the Growth of Fibroblasts in the Healing Wound, *Arch. Surg.* **18**:1227 (April) 1929.

erable difference in the average tensile strength. Actually the wounds of 7 rats in the vitamin B-deficient group and of 7 rats in the control group withstood a pressure of 300 mm. of mercury, indicating that a deficiency of vitamin B complex

TABLE 1.—*Gain or Loss of Body Weight and Tensile Strength of Wound in Normal Adult Control Animals*

Rat	Percentage of Total Body Weight Gained or Lost During Experiment	Tensile Strength of Wound, Mm. of Mercury
Group 1A.—Killed on the Eighth Postoperative Day		
1.....	— 1	300
2.....	— 1	300
3.....	— 1	240
4.....	+ 1	300
5.....	— 2	260
6.....	— 2	300
Group 1B.—Killed on the Tenth Postoperative Day		
1.....	+ 2	300
2.....	— 3	270
3.....	+ 5	300
4.....	— 1	270
5.....	— 4	300
6.....	— 4	270
Average.....	+ 1	285

TABLE 2.—*Gain or Loss of Body Weight and Tensile Strength of Wound in Adult Rats Given a Diet Deficient in Vitamin B*

Rat	Percentage of Total Body Weight Gained or Lost During Experiment	Tensile Strength of Wound, Mm. of Mercury
Group 2A.—Killed on the Eighth Postoperative Day		
1.....	—36	120
2.....	—46	200
3.....	—19	300
4.....	—35	220
5.....	—27	300
6.....	—34	210
Average.....	—33	225
Group 2B.—Killed on the Tenth Postoperative Day		
1.....	—41	300
2.....	—23	300
3.....	—43	280
4.....	—41	300
5.....	—13	300
6.....	—42	300
Average.....	—34	296

has little if any effect on wound healing if the results from the animals tested on the eighth day and on the tenth day are averaged together as though for a single group.

It is interesting to note that the number of wounds attaining strength enough to resist a pressure of 300 mm. of mercury was less and that the average breaking

point of the wounds was at a lower pressure in the rats on a vitamin B-deficient diet killed on the eighth postoperative day than in the control group. These figures, however, are not sufficiently striking to be outside the range of experimental error.

EXPERIMENTS TO DETERMINE EFFECT OF A LOW CALORIC DIET ON WOUND HEALING

Although we did not believe that it would be fair to conclude from the figures just given that a deficiency of vitamin B retarded the early stages of wound healing, we were unable to exclude this possibility and therefore undertook the study of a second control group. The animals in this group were given a low caloric diet designed to effect a loss of weight equivalent to the weight lost by the vitamin B-deficient rats in group 2. This diet consisted of one half of the diet used in the normal controls (group 1) and contained adequate vitamins to prevent deficiency.

TABLE 3.—*Gain or Loss of Body Weight and Tensile Strength of Wound in Adult Rats Given a Low Caloric Diet*

Rat	Percentage of Total Body Weight Gained or Lost During Experiment	Tensile Strength of Wound, Mm. of Mercury
Group 3A.—Killed on the Eighth Postoperative Day		
1.....	—26	300
2.....	—48	300
3.....	—31	240
4.....	—37	180
5.....	—32	200
6.....	—37	270
Average.....	—35	248
Group 3B.—Killed on the Tenth Postoperative Day		
1.....	—32	180
2.....	—34	200
3.....	—43	270
4.....	—31	300
5.....	—33	300
6.....	—48	170
Average.....	—36	236

In this group the wounds were less solidly healed on both the eighth and the tenth postoperative day than in the control group. Moreover, the number of wounds which resisted a pressure of 300 in the rats killed on the eighth postoperative day was exactly equal to that in the vitamin B-deficient group on the same day. These findings indicate that if a deficiency of vitamin B complex has any deleterious effect on wound healing, this effect is probably associated with the loss of weight which accompanies the deficiency rather than the result of the vitamin B deficiency itself. In short, loss of weight, whether due to vitamin deficiency or to deficiency in caloric intake, appears to cause some delay in wound healing.

COMMENT

Abdominal wounds in normal adult control rats were healed with equal strength on the eighth and the tenth postoperative day. The rats neither gained nor lost weight during the experiment.

Rats maintained on a diet deficient in vitamin B complex lost 33 to 34 per cent of their original weight, and on the eighth postoperative day their wounds were not as well healed as those of the controls. On the tenth postoperative day, however, these wounds were healed as solidly as the wounds of the animals in the control group.

Rats maintained on a low caloric diet lost 35 to 36 per cent of their original weight, and on both the eighth and the tenth postoperative day their wounds had failed to heal as well as those of the controls.

On the eighth postoperative day the strength of the wounds was practically the same in the vitamin B-deficient group and in the group maintained on a low caloric diet.

There seemed to be no correlation between the appearance of the wound and its tensile strength. No peritonitis was noted in any of the rats. Histologic examination of the wounds showed only the presence or the absence of surface infection and failed to reveal any apparent cause for the difference in tensile strength of the wounds in the different groups.

CONCLUSIONS

In adult albino rats a deficiency in vitamin B complex has little effect on wound healing.

The slight diminution in the tensile strength of the wounds in vitamin B-deficient rats killed on the eighth postoperative day is probably explained by factors associated with their loss of weight rather than by any specific effect of the vitamin deficiency.

Wound healing in the albino rat appears to be more closely related to changes in body weight than to deficiencies of the vitamin B complex.

STIMULATION OF THE CELIAC PLEXUS IN THE DOG

II. FACTORS INFLUENCING CARDIOVASCULAR AND RESPIRATORY RESPONSES

S. J. MARTIN, M.D.

C. L. BURSTEIN, M.D.

AND

E. A. ROVENSTINE, M.D.

NEW YORK

In a previous report,¹ it was shown that mechanical and faradic stimulation of the celiac plexus in the dog is usually followed by a predominant response characterized by a rise in the mean arterial and venous pressures, a decrease in the pulse pressure, sinus tachycardia and apnea followed by polypnea or a gradual return to normal respiration. It was pointed out also that certain factors, such as the strength of the stimulation applied and the anesthetic drugs employed, influence the character of this response. Stimulation of the sympathetic system may play an important role. An attempt is made in the present investigation to determine (1) the role of other factors, such as premedication, depth of anesthesia and curarization, on the appearance of the predominant response to stimulation of the celiac plexus in the dog and (2) the nature of the mechanism involved.

PROCEDURE

In a group of 19 adult dogs under anesthesia induced with ether, cyclopropane or chloralose,² the celiac plexus, the left splanchnic and right vagal nerves were exposed and prepared for mechanical and faradic stimulation; the strength of the stimuli was kept uniform. Other procedures were completed for recording the arterial blood pressure and respiratory changes.¹

Circulatory and respiratory changes from celiac plexus stimulation were noted as follows: (1) before premedication; (2) one hour after the subcutaneous administration of morphine sulfate (5 mg. per kilogram of body weight) or (3) atropine sulfate (0.05 to 0.1 mg. per kilogram) or (4) both drugs. The dogs

From the Division of Surgery, Department of Anesthesia, New York University College of Medicine.

1. Martin, S. J.; Burstein, C. L., and Rovenstine, E. A.: Stimulation of the Celiac Plexus in the Dog: I. Cardiovascular and Respiratory Effects, *Arch. Surg.* **44**:943 (May) 1942.

2. Chloralose is a preparation of chloralose (a compound of chloral hydrate and dextrose) which has been purified of parochloralose and other impurities.

used for these observations were subsequently employed in the studies hereinafter noted.

Six dogs were anesthetized with ether or cyclopropane after premedication with morphine and atropine. The depth of anesthesia was varied from light (plane 1) and medium (plane 2) to deep (plane 4) levels to determine the significance of this factor on the predominant response to stimulation of the celiac plexus.

The influence on the response to stimulation of the celiac plexus of a purified curare preparation³ (0.07 to 0.5 mg. per kilogram) given intravenously or of a 4 per cent solution of procaine hydrochloride topically applied was investigated in 6 animals.

Special surgical procedures were carried out on 7 dogs; these consisted of (1) bilateral lumboadrenal vein ligation, (2) a spinal block with procaine hydrochloride (150 mg.) or pontocaine hydrochloride (20 mg.) to the level of the second to the fourth thoracic segment and (3) a spinal cord section at the level of the second cervical vertebra.

In all experiments, control records of the mean arterial and pulse pressures and of the rate and amplitude of respirations were compared with those taken during and after the various procedures already cited.

RESULTS

Modifying Factors.—(a) Premedication: A series of fourteen observations revealed that mechanical or faradic stimulation of the celiac plexus in etherized dogs (plane 2) when there had been no preanesthetic medication or when morphine sulfate had been given usually elicited either no change in the cardiovascular or respiratory systems or occasionally a slight rise in the mean arterial blood pressure (10 to 30 mm. of mercury), a small decrease in the pulse pressure (2 to 10 mm. of mercury) and short apnea. However, when stimulation followed the administration of atropine sulfate, alone or with morphine, the characteristic predominant responses in circulation and respiration were noted (figs. 1 and 2).

(b) Curare: The intravenous administration to 4 etherized dogs of a purified curare preparation in amounts adequate to produce intercostal paralysis did not prevent the rise in the blood pressure previously noted following mechanical and faradic stimulation of the celiac plexus or the proximal end of the cut left splanchnic nerve. However, a marked diminution in the magnitude of the response was noted. The rise in the mean arterial blood pressure averaged 10 mm. of mercury; a slight transient fall in the blood pressure occasionally preceded the rise. Further, the decrease in the pulse pressure was negligible. Stimulation of the abdominal vagus nerve was without effect.

Mechanism Involved.—(a) Procaine Hydrochloride Topically Applied: Ten minutes after the topical application of 4 cc. of a 4 per

3. Intocostrin, 1 cc. containing a potency equivalent to 10 mg. of curarc, was supplied by E. R. Squibb & Sons.

cent solution of procaine hydrochloride to the celiac plexus, tension on the viscera of the upper part of the abdomen or mechanical and faradic stimulation of the celiac plexus failed to produce any cardiovascular and respiratory change in ten observations of 2 etherized dogs. The effect of the procaine hydrochloride lasted not less than seventy minutes. It thus seems that all reflex pathways from the viscera of the upper part of the abdomen pass through the celiac plexus and that they can be blocked by the application of procaine hydrochloride to that region.

(b) Bilateral Lumboadrenal Vein Ligation: Bilateral lumboadrenal vein ligation was performed on 2 etherized dogs (plane 2) to determine

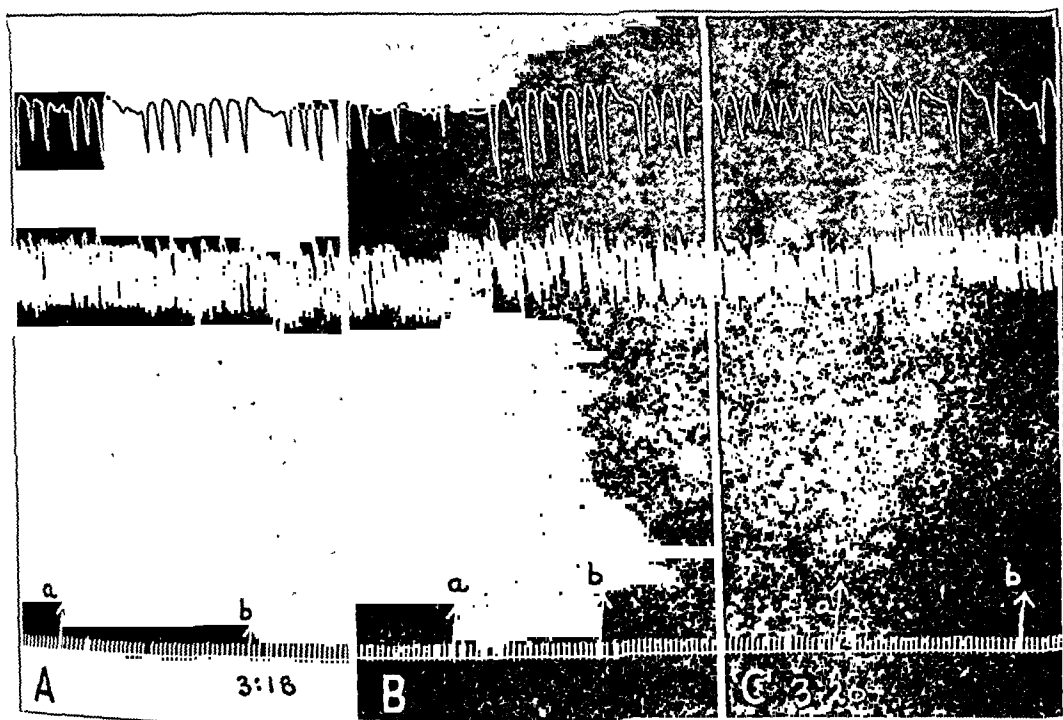


Fig. 1.—Tracings showing the results of faradic stimulation of the celiac plexus (A) and the proximal ends of the cut left splanchnic nerve (B) and the right abdominal vagus nerve (C) of an etherized dog given only morphine premedication. Note the slight or negligible effects on respiration and blood pressure. The upper, middle and lower tracings represent respiration, blood pressure and time in second intervals, respectively; the period of stimulation is noted between arrows.

the influence of the secretion of epinephrine on the predominant cardiovascular and respiratory response following stimulation of the celiac plexus. It was found that such a procedure had little or no significant effect on the appearance of the usual circulatory and respiratory response following mechanical or faradic stimulation of the plexus. In 3 instances the arterial pressure increase was of shorter duration and not as great as the control levels taken prior to ligation of the veins.

(c) *Spinal Anesthesia and Section of the Spinal Cord:* In 3 dogs under anesthesia induced with chloralosane (80 to 90 mg. per kilogram), procaine hydrochloride or pontocaine hydrochloride was injected subdurally to produce anesthesia to the level of the second to the fourth thoracic nerve segments. Intercostal muscles were paralyzed, and only diaphragmatic excursions maintained respiration. It was noted consistently that the cardiovascular and respiratory changes noted in control records after mechanical and faradic stimulation of the celiac plexus or on visceral tension were absent when such stimulation was employed during spinal anesthesia.

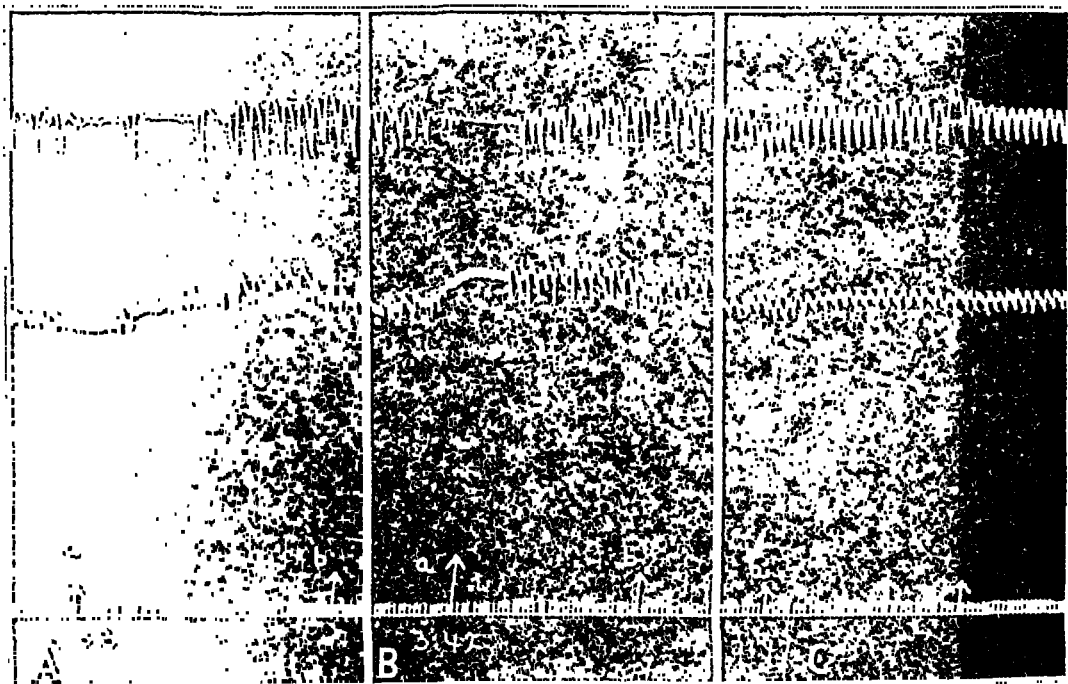


Fig. 2.—Tracings of a dog given the same treatment as the dog whose tracings are shown in figure 1 except that atropine sulfate was given one hour before stimulation. Note the apnea, the rise in the mean arterial blood pressure and the decrease in the pulse pressure after faradic stimulation of the celiac plexus (A) and the splanchnic nerve (B). No change followed stimulation of the abdominal vagus nerve (C).

The spinal cord was sectioned at the level of the second cervical vertebra in 2 dogs, and the respirations were artificially controlled. The afferent path from the celiac plexus was thus destroyed, while the efferent path from this region was left intact. Neither mechanical nor faradic stimulation of the celiac plexus nor visceral tension produced any change simulating the predominant cardiovascular and respiratory effects noted prior to section of the cord.

COMMENT

It was reported that stimulation of the celiac plexus in the dog resulted in a predominant cardiovascular and respiratory pattern. The same study suggested that certain factors, other than the type and the strength of the stimuli, may play an important role.¹ The data in the present investigation illustrate the significance of premedication with atropine in facilitating the appearance of the rise in the arterial pressure, the decrease in the pulse pressure and, to a less extent, the onset of apnea following stimulation of the celiac plexus. The parasympatholytic action of atropine apparently imbalances autonomic equilibrium and enhances sympathetic influences. Such supposed imbalance has been accepted as the rational basis of premedication with physostigmine salicylate to prevent deleterious responses to visceral stimulation.⁴

The depth of anesthesia similarly is of great importance in facilitating the response to stimulation of the celiac plexus. Changes in the levels of anesthesia did not reverse the nature of the cardiovascular and respiratory pattern but merely changed the magnitude of the pattern. The depth of anesthesia is only to be emphasized as another factor to reckon with in seeking uniform results in stimulation of the celiac plexus.

Curarization to the point of intercostal paralysis in anesthetized dogs did not eliminate the rise in the blood pressure that follows stimulation of the celiac plexus. Hence, the effect that changes in respiration or the elimination of efferent intercostal stimuli may have on the predominant response after celiac plexus or visceral stimulation appears to be ruled out. Changes in respiratory activity, therefore, are not primarily responsible for the circulatory effects; however, they can augment them. It must be emphasized that curarization up to the point of intercostal paralysis differs from plane 4 anesthesia in that the central nervous system is not depressed in the former procedure and hence stimulation of the celiac plexus can elicit reflex changes.

The mechanism involved in the cardiovascular and respiratory changes following stimulation of the celiac plexus appears to depend essentially on the integrity of the sympathetic nervous system. This was suggested previously when it was noted that such responses were not affected by severing the abdominal vagus nerve but were markedly diminished after stimulation of the celiac plexus following section of the left splanchnic nerve. Further studies substantiated this contention. Thus, (1) topical application to the celiac plexus of procaine hydrochloride to block all reflex stimuli prevented changes in circulation and respiration when the plexus or the viscera of the upper part of the abdomen were stimulated; (2) blocking of the entire path by high spinal

4. Garrelon, L.; Pascalis, G., and Thuillant, L.: *Presse méd.* **38**:1365, 1930.

anesthesia similarly resulted in no changes in circulation or respiration following stimulation of the celiac plexus, and (3) section of the spinal cord, whereby the afferent reflex path was eliminated and the peripheral efferent path left intact from the celiac plexus, likewise produced no circulatory or respiratory changes on plexus stimulation. It is particularly significant that the parasympathetic path from the region of the viscera of the upper part of the abdomen or the celiac plexus was not disturbed by spinal anesthesia or section of the spinal cord. It may be concluded, therefore, that responses to stimulation of the celiac plexus or stimulation of the viscera of the upper part of the abdomen depend essentially on an intact sympathetic pathway. The experiments concerned with lumboadrenal vein ligation demonstrate the fact that the secretion of epinephrine is not necessary for the appearance of the responses to stimulation of the celiac plexus. The mechanism, while sympathetic in origin, is fundamentally neural and not hormonal.

SUMMARY AND CONCLUSIONS

Mechanical and faradic stimulation of the celiac plexus of dogs under anesthesia induced with ether or cyclopropane is followed by a rise in the mean arterial pressure, a decrease in the pulse pressure, sinus tachycardia and apnea. The appearance of such predominant changes is markedly facilitated by the use of atropine sulfate for preanesthetic medication. Morphine as a premedicant exerts no such influence.

The cardiovascular and respiratory effects following celiac plexus stimulation become magnified during light (plane 1) anesthesia and may be completely eliminated during deep (plane 4) anesthesia.

Curarization of etherized dogs up to the point of intercostal paralysis diminishes the response to stimulation of the celiac plexus but does not eliminate it.

Topical application of solution of procaine hydrochloride to the celiac plexus, spinal anesthesia or high section of the spinal cord eliminates circulatory and respiratory changes following faradic stimulation of the celiac plexus or application of tension to the viscera of the upper part of the abdomen.

The characteristic response to stimulation of the celiac plexus is dependent on afferent reflex stimulation of the sympathetic nervous system. It is augmented by respiratory changes or by any secretion of epinephrine that may result from such stimulation.

HEMOSTATIC EFFECT OF OXALIC ACID

CLINICAL AND EXPERIMENTAL RESULTS, WITH A REVIEW OF THE
LITERATURE

ALEXANDER W. BLAIN, M.D.

Professor of Clinical Surgery, Wayne University College of Medicine

AND

KENNETH N. CAMPBELL, M.D.

DETROIT

Despite normal coagulation and ordinarily careful hemostasis, sufficient blood may be lost during and following operative procedures, chiefly from capillary oozing, to produce such complications as serum collection, wound infection and disruption and even postoperative shock. Delayed convalescence often results. If during or immediately after operation, a drug could safely be administered to the patient which would definitely hasten coagulation, it would constitute a valuable adjunct to mechanical hemostasis and an important advancement in operative surgery. This is true when the coagulation time is normal and more particularly so when it is delayed.

Several commercial products claimed to accelerate blood coagulation have been available for some time. Aggeler and Lucia,¹ in a recent biologic assay of seventeen of these products, found that nine were practically inactive in vitro. The only products found to be significantly active were those suitable for local or oral use. It can readily be deduced, therefore, that before the hemostatic effect of any substance is generally accepted, it must withstand severe clinical and experimental investigation.

In 1939, Steinberg and Brown² found that extracts prepared from certain plants containing oxalic acid accelerated the rate of blood coagulation. On employing pure solutions of oxalic acid, they found that as little as 2 mg. when administered to rabbits was sufficient to reduce the clotting time as much as 50 per cent within fifteen minutes and that it remained reduced for one hour or more. Optimal effects were obtained with 10 mg. of oxalic acid (table 1).

From the Department of Surgery, Alexander Blain Hospital.

1. Aggeler, P. M., and Lucia, S. P.: The Potency of Blood Coagulating Substances: A Biologic Assay, *Am. J. M. Sc.* **199**:181, 1940.

2. Steinberg, A., and Brown, W. R.: A New Concept Regarding the Mechanism of Clotting and the Control of Hemorrhage, *Am. J. Physiol.* **126**:638, 1939.

Steinberg and Brown pointed out also that the administration of an excessive amount of oxalic acid to animals causes calcium depletion, a prolongation of clotting time and finally death, while the administration of small amounts reduces the coagulation time even in hirudinized animals. They concluded that oxalic acid is therefore antagonistic to antithrombin and emphasized that in vivo and in vitro experiments are not comparable, as has been demonstrated many times. This statement was adequately supported by the work of Hammarsten,³ Horne,⁴ Vines⁵ and Scott and associates.⁶

The hemostatic extracts investigated by Steinberg and Brown² were subsequently used in several thousand clinical cases with satisfactory results. Schumann⁷ found that plant extracts containing oxalic acid were effective in the treatment of postpartum hemorrhage and uterine bleeding. Later he treated patients with oxalic acid solution and obtained uniformly good results. Segal⁸ treated a variety of patients exhibiting hemorrhage or hemorrhagic dyscrasia with both plant extracts and oxalic acid and obtained fairly rapid control of the bleeding. Milliken⁹ reported the use of a plant extract in clearing the field of operation for transurethral prostatic resection and felt that it greatly facilitated the operative procedure. Recently, Jackson¹⁰ discussed the use of plant extracts and an oil solution of the ethyl esters of dibasic acids in the treatment of gastrointestinal hemorrhage and noted a satisfactory response. Steinberg, in a personal communication, reported satisfactory results in 160 patients exhibiting bleeding tendencies. Included in this series were cases of hemophilia, jaundice, purpura, leukemia and uterine bleeding. A subsequent article by Steinberg and co-workers¹¹ cited the results obtained in several hundred cases in which the patients were carefully followed.

3. Hammarsten, O.: The Clotting of Fibrin, *Arch. f. d. ges. Physiol.* **14**:211, 1877.

4. Horne, R. M.: The Action of Strontium, Barium and Calcium Salts in Preventing Coagulation of Blood, *J. Physiol.* **19**:356, 1896.

5. Vines, H. W. C.: The Role of Calcium in Blood Coagulation, *J. Physiol.* **55**:86, 1921.

6. (a) Scott, F. H., and Chamberlain, C.: Calcium and Blood Coagulation, *Am. J. Physiol.* **91**:27, 1930. (b) Scott, F. H., and Loucks, N. M.: Calcium and Blood Coagulation, *Proc. Soc. Exper. Biol. & Med.* **31**:1054, 1934.

7. Schumann, E. A.: Newer Concepts of Blood Coagulation and the Control of Hemorrhage, *Am. J. Obst. & Gynec.* **38**:1002, 1939.

8. Segal, H. I.: Personal communication to the authors.

9. Milliken, L. F.: The Use of a New Blood Coagulant in Transurethral Prostatic Resection, *J. Urol.* **42**:75, 1939.

10. Jackson, A. S.: Editor's Comments, *Jackson Clin. Bull.* **2**:3, 1940.

11. Steinberg, A.; Segal, H. I., and Parris, H. M.: Role of Oxalic Acid and Certain Related Dicarboxylic Acids in Treatment and Control of Hemorrhage, *Ann. Otol., Rhin. & Laryng.* **49**:1008, 1940.

The suggestion that oxalic acid promoted coagulation was rather startling and seemed paradoxical, since the oxalates are well known anti-coagulants *in vitro*. However, in the past decade approximately one hundred and seventy-five articles dealing with the pharmacology and metabolism of oxalic acid have appeared in the medical literature. One hundred and forty-five of these articles appeared in Italian, German, Japanese and French periodicals; only a few were published in American or English journals.

Suzuki's¹² method for the quantitative determination of oxalic acid in blood was modified by Steinberg, and by this method normal values for human beings were established between 5.5 and 7.5 mg. per hundred cubic centimeters of blood and for rabbits between 2.5 and 6.0 mg. Other investigators¹³ have placed the normal blood level of oxalic acid in human beings between 2 and 8 mg. per hundred cubic centimeters of blood. These values have been confirmed by us, using the Steinberg modification.

METABOLISM OF OXALIC ACID

It is generally believed that oxalic acid is dangerously poisonous. MacKenzie and McCollum¹⁴ stated that the smallest recorded lethal dose of oxalic acid for man, administered orally, is 4 Gm. and quoted Koch to the effect that 3 Gm. of oxalic acid, given by stomach tube, is the lethal dose for cats and 1.8 Gm., for rabbits. About one eighth of these doses were lethal when injected parenterally. Many commonly administered drugs are much more highly toxic than oxalic acid.

In an attempt to produce oxalate nephritis experimentally in dogs, Arnott and Kellar¹⁵ experienced some difficulty, even with repeated doses of as high as 100 mg. of sodium oxalate. Even with such large doses, histologic glomerular lesions could not be produced, although albuminuria was noted. Likewise no degenerative changes in the liver were produced.

That oxalemia is an accompaniment of any form of hyperglycemia has been demonstrated on several occasions by many investigators, among

12. Suzuki, S.: Glucose as a Source of Oxalic Acid, *Jap. J. M. Sc.*, II, *Biochem.* **2**:401, 1934; Adrenalin and Insulin as Factors Causing Variations in Oxalic Acid Level, *ibid.* **3**:23, 1935.

13. (a) Muller, P. B.: Oxalic Acid Metabolism in Man and Animals, *Schweiz. med. Wchnschr.* **68**:964, 1938. (b) Schumann.⁷ (c) Scott and Chamberlain.^{6a} (d) Segal.⁸

14. MacKenzie, C. J., and McCollum, E. V.: Some Effects of Dietary Oxalate on the Rat, *Am. J. Hyg.* **25**:1, 1937.

15. Arnott, W. M., and Kellar, R. J.: Hypertension Associated with Experimental Oxalate Nephritis, *Brit. J. Exper. Path.* **16**:265, 1935.

them Oikawa,¹⁶ Viale,¹⁷ Muller,^{13a} Pennetti¹⁸ and de Lucia.¹⁹ De Lucia confined his observations to the elimination of oxalic acid in cases of oxalemia produced by the administration of glucose, either oral or subcutaneous, or by the injection of epinephrine. These experiments were performed on dogs. It appears from the findings presented by the authors mentioned that with hyperglycemia, irrespective of its origin, there exists an excess of oxalic acid and that the amount of oxalic acid corresponds to the degree of hyperglycemia. Possibly the slight reduction in coagulation time associated with the administration of dextrose or epinephrine to human beings is somewhat related to the oxalemia thereby produced. Muller^{13a} also showed that in experiments in vitro in which dextrose is added to defibrinated blood, there is an increased production of oxalic acid.

Most of the oxalic acid in the blood is excreted in the urine, a smaller amount through the bile and a small quantity in the saliva. It has been noted by several observers that in cases of hepatic insufficiency, diabetes, pregnancy and various other conditions, there occurs a marked disturbance in oxalic acid metabolism. Since there is experimental evidence that oxalic acid may be an important substance in metabolism, correlative clinical investigation might further the knowledge of the possible role of this substance in the coagulation of blood. At the present time, unfortunately, the physical and chemical changes involved are not well understood.

In tables 1 and 2 as well as in charts 1 and 2 are shown the comparable experimental results obtained by Steinberg and by us. In our experiments a solution of recrystallized oxalic acid with a p_H of 3.5 to 4.8 was given intravenously. The maximum dose given to any single rabbit was 140 mg., and this dose failed to produce histologic changes in the kidneys, the liver, the spleen, the pancreas, the skeletal muscles or the gastrointestinal tract when administered over a three day period. Experimentally, maximum effects occur within thirty minutes after administration. Clinically, a response seems to occur much earlier than this. It is of interest that while the quantities of oxalic acid administered to rabbits varied greatly, a maximum of 50 mg. being administered at

16. Oikawa, S.: Hyperoxalemia Induced by Glucose and Adrenalin, *Jap. J. M. Sc., II, Biochem.* **4**:41, 1938; Influence of Exercise on Oxalic Acid Excretion, *ibid.* **4**:17, 1938.

17. Viale, G.: Influence of Insulin on the Metabolism of Oxalic Acid, *J. Nutrition* **3**:111, 1933; Endocrine Influence on the Metabolism of Oxalic Acid, *Rev. sud-am. de endocrinol.* **9**:967, 1926.

18. Pennetti, G.: Oxalemia in Liver Disease, *Riforma med.* **51**:1358, 1935.

19. de Lucia, P.: The Elimination of Oxalic Acid in Various Forms of Hyperglycemia, *Boll. Soc. ital. di biol. sper.* **4**:356, 1929.

one time, practically identical results were obtained. This was observed both clinically and experimentally.

We have found that between 20 and 40 mg. is the optimal dose for human beings. The solution can be administered either intravenously or intramuscularly and may be repeated within a short time. It is difficult to explain why similar effects are produced with variable quan-

TABLE 1.—*Experimental Studies of Coagulation Time Made by Steinberg**

Dose, Mg.	Normal		15 Minutes		30 Minutes		60 Minutes	
	Time	Per Cent	Time	Per Cent	Time	Per Cent	Time	Per Cent
2	153.2	100	132.4	86.4	102.0	66.5	93.4	60.9
4	208.6	100	64.0	30.6	42.0	20.1	55.0	26.3
5	125.8	100	62.0	50.8	34.0	27.0	80.0	63.5
10	112.4	100	42.8	38.0	34.4	30.6	52.9	47.0
50	242.2	100	171.4	70.7	65.0	26.8	167.0	68.9
Average.....				55.3		34		53.3

* This table gives the results obtained by Steinberg from rabbits. The figures represent the time in seconds; percentages given are of the normal values. Note that the greatest reduction in coagulation time occurred in thirty minutes in practically all cases.

TABLE 2.—*Experimental Studies of Coagulation Time Made by Blain and Campbell**

Dose, Mg.	Normal		15 Minutes		60 Minutes	
	Time	Per Cent	Time	Per Cent	Time	Per Cent
2	140.2	100	60.4	43.0	90.6	64.6
4	218.8	100	80.6	36.8	110.8	50.6
5	200.2	100	99.2	49.5	102.8	51.3
10	186.6	100	90.6	48.7	98.8	52.4
Average.....				44.5		54.7

* The figures represent the time in seconds; the normal time is given as the average of ten determinations. Oxalic acid solution (recrystallized, pH 3.5 to 4.8), original acidity reduced with sodium hydroxide, was given by intravenous administration in all cases. Five rabbits were used in this series. Single trials of each dosage were given at daily intervals to each rabbit. The maximum amount given any single animal—140 mg.—failed to produce microscopic lesions in the kidneys, the liver, the spleen, the pancreas, the muscles or the gastrointestinal tract when administered over a three day period. Note that the results closely parallel those of Steinberg.

ties of oxalic acid. Oxalic acid apparently has little or no effect on prothrombin time (table 3).

In the first 100 cases in this series, oxalic acid solution in amounts varying between 20 and 60 mg. was administered more or less routinely to patients before or during operation, and the patients were carefully observed for any deleterious effects. None were detected. The succeeding cases were selected because in them excessive and troublesome oozing was encountered during operation and oxalic acid solution was administered after the operation was begun. A wide variety of surgical

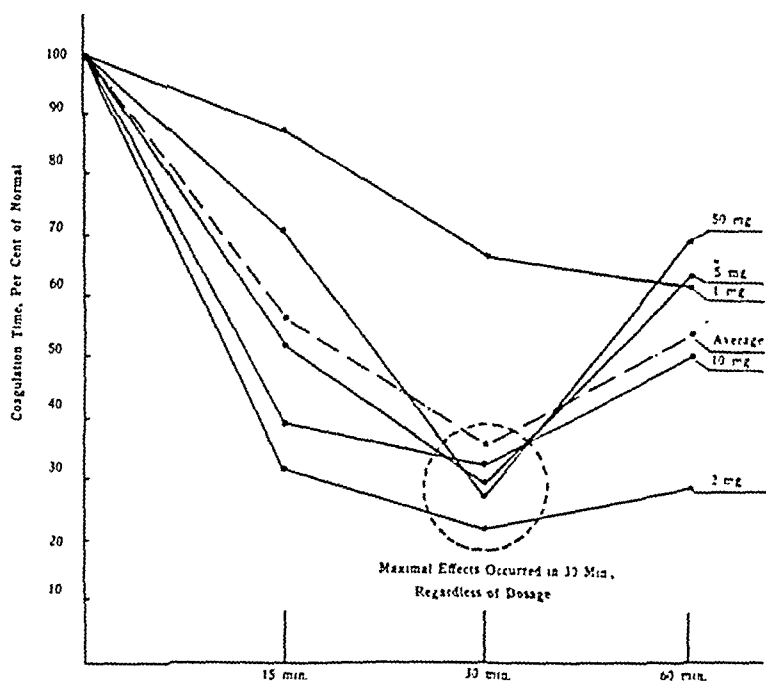


Chart 1.—Graphic analysis of Steinberg's experimental results given in table 1.

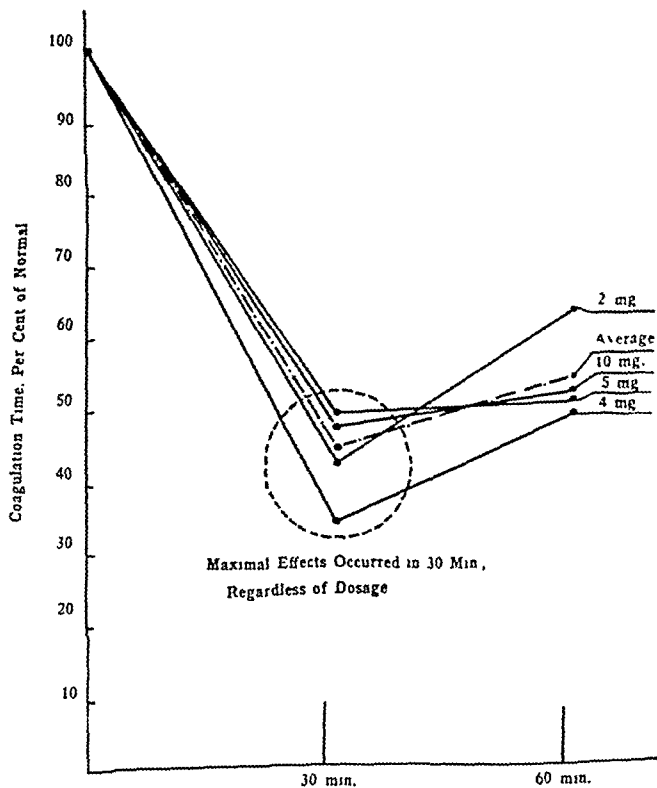


Chart 2.—Graphic analysis of Blain and Campbell's experimental results given in table 2.

procedures was included, and observations were made in the departments of urology and otolaryngology of the hospital as well as in the department of general surgery. In every case the result was recorded as satisfactory or excellent, and in most cases one administration of oxalic acid solution was sufficient to control oozing. Good clot formation occurred, the operative field was made much drier, and secondary hemorrhage was believed to have been prevented. In thyroidectomy, vaginal hysterectomy and cholecystectomy, we have found the practical advantages of this hemostatic agent particularly outstanding. The coagulation time,

TABLE 3.—*Determination of Prothrombin Time Before and After the Administration of Oxalic Acid in Consecutive Cases in Which Operation Was Performed **

Operative Procedure	Prothrombin Time Before Operation (Sec.)	Control Time (Sec.)	Oxalic Acid Administered (Mg.)	Prothrombin Time After Operation (Sec.)	Control Time (Sec.)	Comment
Thyroidectomy.....	18	13	20	16	14	Slight reduction
Cholecystectomy and appendectomy	13	13	40	13	14	No change
Thyroidectomy.....	18	13	20	15	15	Slight reduction
Hemorrhoidectomy....	17	13	20	18	15	No change; minimal increase
Thyroidectomy.....	13	13	20	15	18	Slight increase
Vaginal hysterectomy	15	15	40	14	12	Slight reduction
Thyroidectomy.....	17	15	20	16	12	Slight reduction
Hemorrhoidectomy....	16	15	20	16	12	No change
Herniorrhaphy.....	20	15	20	17	15	Slight reduction
Herniorrhaphy.....	17	12	20	14	14	Slight reduction
Hemorrhoidectomy....	18	12	20	17	14	Slight reduction
Hysterectomy.....	15	12	40	14	14	Slight reduction
Amputation cervix....	12	12	20	13	14	Minimal increase
Amputation cervix....	14	12	20	13	14	Slight reduction
Herniorrhaphy.....	16	12	20	16	14	No change

* Prothrombin values were determined by the Quick method. Oxalic acid was administered during operation.

determined by the method of Lee and White, was decreased in every case, confirming the experimental results to which we have already referred.

The control of bleeding in the operative field by methods other than ligation and electrodesiccation is at present difficult. At times an excessive amount of suture material is introduced into an operative wound, particularly in the thyroid area, in order to get a dry wound, and the use of dextrose solution and the application of hot compresses are time consuming and traumatize tissues. It is in those troublesome cases that after all of the bleeders have been ligated, but capillary oozing continues to a marked degree, the effect of oxalic acid solution has been most dramatic clinically. Postoperative sequelae have been favorably

influenced, particularly wound infection. In our opinion, wound infection occurs not entirely from the introduction of micro-organisms but as well from the collection of blood or serum in wounds. Excessive oozing cannot always be anticipated before operation, and because the drug in the doses given is entirely harmless, we pursue the practice of administering oxalic acid routinely in certain types of major operation. Patients with jaundice and deficiency of vitamin K have not been included in this discussion.

METHOD OF PREPARATION

Since oxalic acid in aqueous solution is unstable at high temperatures, overheating must be avoided in its preparation, and pressure sterilization cannot be utilized. A saturated solution is first prepared by dissolving chemically pure oxalic acid in sterile distilled water at 60 C. This solution is cooled in a refrigerator to 5 C., and the precipitated oxalic acid is filtered. Strict aseptic precautions should be observed in each step. Ten grams of dried recrystallized oxalic acid is then dissolved in 800 cc. of sterile distilled water. One hundred and forty cubic centimeters of normal sodium hydroxide is then added, sufficient distilled water being finally added to bring the volume to 1 liter. The hydrogen ion concentration of this solution then varies between 3.5 and 4.3. The solution is next filtered through a Berkefeld filter, and the finished product is placed in sterile amber ampules or vaccine bottles of a capacity not greater than 5 cc. These ampules or bottles are stored in the refrigerator. A small amount of phenol may be added as a preservative if desired. One cubic centimeter of the finished product contains 10 mg. of oxalic acid.

CLINICAL OBSERVATIONS

In the administration of oxalic acid to 440 operative patients, on whom nearly all major operative procedures were performed, the following observations were made:

1. Either immediate cessation of hemorrhage or a noticeable decrease in oozing occurred in practically all cases.
2. There was a definite measurable reduction in coagulation time.
3. There was no appreciable decrease in prothrombin time.
4. The best clinical results were obtained in those cases in which a large oozing surface constituted the source of hemorrhage.
5. There was no clinically demonstrable renal damage following the administration of oxalic acid.
6. In no case did thrombophlebitis develop after the use of this drug, nor were there any untoward clinical reactions.
7. There was an apparent decrease in the amount of serum collection in the incisional wound.
8. The administration of oxalic acid effectively controlled bleeding associated with carcinoma.

SUMMARY

A sterile aqueous solution of recrystallized oxalic acid has been administered intramuscularly by us in 440 clinical cases to control bleeding incident to surgical procedures and has been found to be a satisfactory hemostatic agent in all circumstances.

It is now used routinely in this hospital as a prophylactic measure against hemorrhage in major surgical procedures in which capillary oozing is anticipated.

The optimal dose for human beings is 20 mg., and this may be repeated if necessary.

Experimental and clinical investigation indicates that the hemostatic effect of oxalic acid is exhibited promptly.

Oxalic acid is a safe, reliable, inexpensive and almost instantly effective hemostatic agent.

2201 Jefferson Avenue, East.

1313 East Ann Street, Ann Arbor, Mich.

REVIEW OF UROLOGIC SURGERY

ALBERT J. SCHOLL, M.D.

LOS ANGELES

FRANK HINMAN, M.D.

SAN FRANCISCO

ALEXANDER VON LICHTENBERG, M.D.

MEXICO, MEXICO

ALEXANDER B. HEPLER, M.D.

SEATTLE

ROBERT GUTIERREZ, M.D.

NEW YORK

GERSHOM J. THOMPSON, M.D.

AND

JAMES T. PRIESTLEY, M.D.

ROCHESTER, MINN.

EGON WILDBOLZ, M.D.

BERNE, SWITZERLAND

AND

VINCENT J. O'CONOR, M.D.

CHICAGO

KIDNEY

Anomalies.—Dees¹ states that developmental anomaly of the kidney or the ureter is of clinical importance and that it occurred among 9.6 per cent of 1,410 consecutive patients for whom pyelograms had been made.

Renal anomaly accounts for much more than 9.6 per cent of diseases of the upper part of the urinary tract.

Symptoms of anomaly of the upper part of the urinary tract usually begin when the patients are between the ages of puberty and 35 years.

Of 135 patients who had renal anomaly, the anomaly was the definite cause of symptoms among 100; it was asymptomatic among 25 and was a questionable cause of symptoms among 10.

Infection was present in 50 per cent of the patients who had renal anomaly; calculus was present in 20 per cent and obstruction in 43.5 per cent.

The chief complaint of 62.2 per cent of the patients was pain of renal or ureteral distribution. The pain was caused by infection, obstruction

1. Dees, J. E.: The Clinical Importance of Congenital Anomalies of the Upper Urinary Tract, *J. Urol.* **46**:659-666 (Oct.) 1941.

or stone in the majority of cases; but it occurred also among 16 patients who had uncomplicated renal anomaly.

The incidence of hypertension in the group was not appreciably different from that which would be noted in an unselected group. In 3 patients, however, the congenital anomaly was felt to be the cause of hypertension.

Thirty-nine patients (29 per cent) required open operation on the kidney or the ureter for correction of the anomaly or its complications.

Shivers and Mathis² present a case representing complete unilateral duplication of the ureter and the pelvis complicated by a cystlike dilatation of the intravesical portion of the supernumerary ureter. This condition was not true ureterocele. Within this dilated portion of the ureter were three calculi. There was no evidence of dilatation of the ureter or the renal pelvis above the site of this obstruction. Histologic study of the tissue removed at operation disclosed that infection was not present, and the evidence pointed to an acute destructive process involving the wall of the ureter and probably, to some extent, the connective tissue of the wall of the bladder surrounding it. This acute process was brought about by mechanical irritation and interference with venous and lymphatic return drainage caused by the calculi. The rapid expansion of the terminal portion of the supernumerary ureter, together with the ability of the muscular structure of the upper part of the ureter and the pelvis to undergo work hypertrophy, probably compensated for any back pressure which may have existed and accounted for the absence of dilatation which might be expected to occur in the upper part of the ureter and the pelvis in the presence of an obstructive lesion in the lower part of the ureter.

Surgical Procedures.—Campbell³ states that there is a conservative surgical treatment of certain renal diseases which are localized to one segment of a normally formed kidney or to a half of a reduplicated, a horseshoe or an otherwise bilaterally fused kidney.

In some instances, the remaining segment of the kidney will prove to be so small as to make resection an unwarranted or unjustifiable surgical risk; in such an instance nephrectomy is required. Occasionally, primary or secondary nephrectomy will be required because of surgical damage to the renal vascular supply.

With due care to adequate preoperative preparation by the administration of fluids, the use of urinary antiseptic agents and particularly

2. Shivers, C. H. deT., and Mathis, J. H.: A Clinical Study of Two Unusual Types of Renal and Ureteral Disease, *J. Urol.* **46**:1079-1099 (Dec.) 1941.

3. Campbell, M. F.: Resection of the Kidney, *J. A. M. A.* **117**:1223-1229 (Oct. 11) 1941.

the transfusion of blood, a gratifying number of both young and older patients can successfully undergo renal resection with conservation of a worth while amount of satisfactorily functioning tissue. The technic of and indications for the various procedures employed are to be considered. The mortality rate accompanying this operation is low, in view of the gravity of the surgical problem. Campbell reports that 2 deaths occurred in 41 cases of resection of the kidney. In 1 case, a child died who had an enormous cyst in the upper part of the pelvis in the right reduplicated portion of a horseshoe kidney. This death, four days after operation, was directly due to surgical trauma (largely, rapid evacuation of the cyst) and to hemorrhage from an aberrant vessel which entered the upper pole of the cystic kidney from a point high under the liver. The other death was attributable to infection of the wound in the loin.

When urinary infection is part of the urologic disturbance, the patient should not be discharged as cured after the operation until at least two negative cultures of an aseptically collected specimen of urine have been obtained.

Campbell has not found any notable changes in the blood pressure of patients who by operation are left with a half of a reduplicated kidney.

Surgical Complication.—Mathé and Faulkner ⁴ report a case of bilateral pneumothorax, mediastinal emphysema and extensive subcutaneous emphysema complicating nephrectomy for tuberculosis. The causative mechanical factors involved in the production of pneumothorax in their case probably were nicking of the visceral (diaphragmatic) pleura; tearing of the right and left mediastinal pleura; fracture of the eleventh rib by the kidney rest and puncture of the underlying lung and rupture of an obstructive emphysematous lung, an emphysematous bleb or tuberculous lesions.

Preexisting pathologic changes within the thorax, such as mobility and friability of the mediastinum and pleuropulmonary adhesions, play a definite role in the prevention or in the indirect production of operative pneumothorax.

The distinguishing feature in the general treatment of unilateral, bilateral, adherent and nonadherent types of pneumothorax is discussed.

Tuberculosis.—Braasch and Sutton ⁵ state that a diagnosis of bilateral renal tuberculosis was made among 291 (13 per cent) of 2,200 patients

4. Mathé, C. P., and Faulkner, W. B., Jr.: Bilateral Pneumothorax and Subcutaneous Emphysema Complicating Nephrectomy: Report of a Case, *J. Urol.* **46**:601-612 (Oct.) 1941.

5. Braasch, W. F., and Sutton, E. B.: Prognosis in Bilateral Renal Tuberculosis, *J. Urol.* **46**:567-578 (Oct.) 1941.

with renal tuberculosis observed at the Mayo Clinic during the years 1910 to 1934, inclusive. Eighty-seven of these 291 patients underwent nephrectomy; hence, 204 patients with tuberculosis did not undergo operation.

Nephrectomy in cases of bilateral renal tuberculosis is indicated only when there is a decided difference in the extent of the process in the two kidneys. Nephrectomy is usually not indicated unless the diseased kidney is the cause of symptoms requiring relief.

A clearcut history of a period of dysuria and frequent micturition many years prior to examination and a recent history of recurrence of symptoms frequently are elicited and are typical of bilateral involvement. When the disease is bilateral, cystoscopic examination usually reveals a greater degree of involvement of the bladder than is found when the disease is unilateral.

The previous occurrence of tuberculosis in other tissues often seems to increase the patient's resistance to renal tuberculosis and may be accompanied by a relatively good prognosis.

In spite of advanced bilateral involvement of both kidneys, the combined renal function often is normal or is only slightly reduced. Little subjective evidence of renal insufficiency was observed in many cases in which renal function was reduced greatly.

The incidence of hypertension in cases of bilateral renal tuberculosis is little higher than the average incidence of hypertension observed among adult persons.

The subsequent clinical course was traced in 167 cases in which definite clinical evidence of bilateral renal tuberculosis was present. The survival rate for patients traced after three years or more was about 72 per cent; for those traced after five years or more, 58 per cent; for those traced after ten years or more, 26 per cent, and for those traced after fifteen years, 16 per cent. Most of the patients who were living ten or fifteen years after examination were in fairly normal condition except for variable degrees of frequency of urination.

Therapeutic measures, such as treatment in a sanatorium or the advantages of rest, diet and sunshine, undoubtedly are factors in aiding longevity.

The authors declare that previous concepts concerning life expectancy in cases of nonsurgical renal tuberculosis demand radical revision. Unless the indications for nephrectomy are definite in a case of bilateral disease, they say, it would be well "to give nature a chance."

Thomas, Stebbins and Sandell⁶ present reports of 4 cases of renal tuberculosis, in which the clinical data indicated that the tuberculous

6. Thomas, G. J.; Stebbins, T. L., and Sandell, S. T.: The Control and Arrest of Lesions of Renal Tuberculosis, *J. Urol.* **46**:579-589 (Oct.) 1941.

process in the kidneys had healed or had become arrested by means of an intensive hygienic regimen. The authors recommend hygienic treatment for all patients who have renal tuberculosis. Their opinion is that kidneys should and do react toward the destructive effect of *Mycobacterium tuberculosis* as do other organs and tissues.

Beach and Shultz⁷ report 8 clinical instances of spontaneous healing of renal tuberculosis as signalized by nonrecurrent objective findings and lack of subjective developments over a prolonged period of observation ranging from six to fifteen years.

Diagnosis depended on recovery of *Myco. tuberculosis* from urine obtained from the kidney and specific identification of this organism. There was never any significant pyelographic change or deformity.

If the presence of *Myco. tuberculosis* in urine obtained from the kidney connotes tuberculous disease in a given kidney, then by the same token, disappearance of this organism from urine obtained from the kidney, without return of the organism for several years, should attest to healing of the erstwhile lesion or lesions, especially in the absence of symptomatic developments.

Since incontestable anatomic evidence avouches that usually only cortical healing occurs, the patients in the cases reported probably suffered cortical lesions.

There is no warranty that these cortical lesions under less favorable circumstances cannot undergo reactivation and extend into the medulla, only to culminate in renal or operative tuberculosis.

Ureterostomy for Renal Tuberculosis.—Higgins⁸ states that the major complication which ensues after the performance of cutaneous ureterostomy is sloughing of that portion of the ureter which protrudes beyond the skin. Immediate application of warm saline dressing to the stump of the ureter and keeping it in place for several days after the performance of cutaneous ureterostomy may prevent such sloughing.

The ureter should not be stripped, because it must be made certain that an adequate blood supply to the ureter itself is maintained. Also, the ureter should be freed down toward the bladder as far as possible, so that tension on the portion of the ureter that protrudes beyond the skin can be avoided when the ureter is brought out at this site. This, of course, obviates the necessity of suturing the ureter to the skin and further impairing the blood supply. After cutaneous ureterostomy has been done, a small ureteral catheter should be passed up the pelvis of

7. Beach, E. W., and Schultz, W. G.: Spontaneous Healing in Renal Tuberculosis, *J. Urol.* **46**:590-600 (Oct.) 1941.

8. Higgins, C. C., in discussion on papers of Smith,²⁹ Colby²⁷ and Creevy,³¹ *Tr. Am. A. Genito-Urin. Surgeons* **34**:123-124, 1941.

the kidney and left in situ for a few days. The stump of the ureter and the catheter should be surrounded with moist saline dressings. This prevents leakage of urine at the operative site.

Stones.—Kjølhed and Lassen⁹ state that on the basis of their own results of examination of kidneys in 135 cases in which necropsy was carried out as compared to the description by Randall himself of deposits of calcium on the papillae, they cannot see that Randall's papillary lesions are new pathologic entities.

In 86 of 135 cases in which necropsy was done, they found several kinds of deposits of calcium salts in the kidneys. In 14 instances, they discovered calculi in the kidneys, but only once did a papillary deposit of calcium salt seem to have contributed to the development of a coexisting calculus.

Since calculi often are found in kidneys without such deposition, the authors say that the deposits of calcium salt cannot be of essential significance in the genesis of calculi. In 4 cases, stone was found attached to the mucous membrane of a calix outside the renal papilla, but this stone had not developed from deposits of calcium there. Such deposits, however, are now and then encountered in the mucous membrane of a calix.

The deposits found occurred independently of the factors of sex and age of the patients affected, and also seemed to have had no relation to diseases of the gastrointestinal tract, the liver or the circulatory system; they were, however, encountered relatively often in association with such diseases as arteriosclerosis, infection or stasis in the kidneys.

Kjølhed and Lassen declare that according to Randall, it should be considered as proved that deposits of calcium on the surface of a renal papilla constitute the starting point of the formation of calculi. However, results of their study indicate clearly that such papillary deposits cannot be causes of any great significance in the genesis of calculi since it was possible in only 1 case in their series to demonstrate a calculus which might have been adherent to such a deposit. Their conclusion is that a deposit of calcium salts at the most can be a *locus minoris resistentiae* in the development of renal calculi but that such development most frequently is the result of other wholly different factors.

Derrah and Kaufman¹⁰ present 2 cases in which calculosis of the right kidney was associated with obstructive jaundice. Obstructive jaun-

9. Kjølhed, K. T., and Lassen, H. K.: The Significance of Randall's Papillary Lesions in the Causation of Renal Calculi, *J. Urol.* **47**:45-57 (Jan.) 1942.

10. Derrah, B., and Kaufman, D. R.: Disease of the Right Kidney as a Cause of Obstructive Jaundice: An Anatomical Explanation, *J. Urol.* **46**:853-865 (Nov.) 1941.

dice and vague gastrointestinal symptoms without jaundice may be caused by renal disease on the right. The close anatomic relationship of the right kidney to the duodenum as well as the renal digestive reflex should be considered when an attempt is made to account for gastrointestinal symptoms of renal disease on the right.

Hyams and Kenyon¹¹ state that urinary calculi are not infrequently symptomless and are therefore overlooked. Since many calculi are present for a long time before detection, they are of large size when they are finally found and are accompanied by advanced changes in the kidney. A history of previous calculosis with persistent infection of the urinary tract by urea splitting organisms in spite of intensive treatment necessitates frequent urographic observation. As progress in medicine continues and as improved diagnostic measures are devised and routine roentgen studies are carried out, many instances of this type of calculus may be detected before irremediable damage has ensued.

Tumor.—Study of reports of treatment in cases of Wilms's tumor shows that there are well qualified adherents of three types of therapy: operation, radiation and a combination of operation and radiation. Dean¹² states that Wilms's tumor is so rare that the majority of urologists and pediatricians encounter it only occasionally, but he declares that they do recognize the seriousness of the condition.

Wilms's tumor is a congenital embryonic mixed tumor which originates from the anlage of the kidney. Depending on the stage of embryonic development at which the tumor arises, its structure may vary considerably in the degree of differentiation of its component cells and in the number of different tissues represented. These structural differences probably are the principal reasons for wide variations in the natural history and the radiosensitivity of Wilms's tumor and in the clinical course of the patient who has it.

Dean reports the results of the treatment of 8 patients. Widely different results were obtained. In view of clinical experiences such as he discusses in which the disease seldom follows the same course and responds so differently to similar forms of treatment, he is of the opinion that it is misleading to consider Wilms's tumor a clinical entity with a uniform mode of onset or a natural history which follows a common pattern and which regularly responds to the same treatment.

Since in most cases the disease is far advanced when the first symptom occurs, no time should be lost in establishing the diagnosis.

11. Hyams, J. A., and Kenyon, H. R.: Silent Urinary Calculi, *Urol. & Cutan. Rev.* **44**:230-235 (April) 1940.

12. Dean, A. L.: The Treatment of Wilms' Tumors, *Tr. Am. A. Genito-Urin. Surgeons* **34**:75-79, 1941.

Excretory urograms, therefore, should be made whenever there is the suggestion of a mass in the region of an infant's kidney.

As soon as the primary tumor has been demonstrated, every part of the body should be searched for metastasis. If any is found, the patient cannot be operated on. The scalp seems to be a favorite site for early spread of the process. Even when the lungs appear to be normal at first, roentgenograms of the thorax should be made repeatedly every two to three weeks.

Dean expresses the opinion that the treatment of every Wilms's tumor should begin with irradiation. This should continue as long as the tumor shrinks. Since the minimal curative dose for individual tumors is unknown, it is essential to treat each patient without interruption to full skin tolerance. Although marked regression often occurs, the tumors always regenerate. Like many other therapeutic agents, external radiation must be given Wilms's tumor until the desired effect has been accomplished.

If radioresistance is demonstrated by failure of the tumor to regress after two weeks of daily irradiation, surgical intervention should be employed without further delay. The best operation for a large tumor seems to be carefully and gently performed transperitoneal nephrectomy after the vessels of the renal pedicle have been ligated. In addition to these principal vessels, a number of dilated veins are often found which pass from the periphery of the tumor to adjacent perirenal tissues. It is well to cut these between double ligatures. After removal of the kidney, a search should be made for extrarenal extension, but, as Dean's records show, they are not always discovered when they are present. For this reason it is wise to give radiation postoperatively.

Kirwin¹³ presents and discusses a case in which the papillary tumor involved the renal pelvis. Complete nephroureterectomy was done, together with removal of a coned-out segment of that part of the wall of the bladder surrounding the ureter. Results achieved in his case provide ground for the belief that no time should be wasted in the application of roentgen therapy. Coutard's method of fractional dosage was attempted, but the patient proved unable to endure it.

Papillary carcinoma of the renal pelvis is a relatively uncommon form of neoplasm, although a steadily increasing incidence seems to be indicated by the number of reports concerning it which have appeared recently in medical literature. This is due, however, not so much to actual increase in the number of cases, as to improvements in urologic

13. Kirwin, T. J.: Papillary Carcinoma of the Renal Pelvis. *Surg., Gynec. & Obst.* 73:759-765 (Dec.) 1941.

diagnostic methods, which permit more frequent recognition of the lesion.

Hager and Schiffbauer¹¹ present a case in which a metastatic lesion in the wall of the chest became evident eight years before the primary renal adenocarcinoma was extirpated. The patient was well two years after removal of the primary and secondary tumors. "In all probability had our information been complete in the beginning, surgery might have been denied the patient," the authors write. They say that their experience bears out Barney's contention that "if a metastasis is apparently solitary and accessible to surgical removal, it is definitely worth while to undertake removal of the metastasis as well as the primary growth."

Foulds¹⁵ records a case in which a renal tumor contained elements of malignant papillary cystadenoma and papillary carcinoma with clear cells. This case, with other reported cases, illustrates the transition from renal adenoma to malignant cystadenoma and eventually, in some instances, to papillary carcinoma with clear cells.

Polycystic Disease.—In a series of 58 patients with polycystic renal disease seen by Cahill and Fish,¹⁶ operative procedures were carried out for 23. The age of these patients ranged from 3½ months to 74 years. The average age was 40 years.

Conditions in which operation is required may well be divided into six groups, as follows: (1) severe hemorrhage within or around the kidney, caused by physical trauma to the kidney, such as blows and falls or spontaneous rupture of cysts; (2) infection within or around the kidney; (3) obstruction to the flow of urine caused by pressure of cysts within the kidney or the ureters; (4) obstruction or pain caused by calculi; (5) tumors and tuberculosis which are producing actual destruction of the kidney, and (6) steadily increasing hypertension without other evidence of renal failure.

When polycystic renal disease has progressed to a point at which renal failure or impending renal failure is due to the disease itself, the prognosis is poor, and the results of most operative procedures are unsatisfactory. When symptoms, such as pain, hematuria, anuria, gastric

14. Hager, B. H., and Schiffbauer, H. E.: Silent Adenocarcinoma of the Kidney with Single Metastasis to the Chest: Report of a Case, *Tr. Am. A. Genito-Urin. Surgeons* **34**:1-7, 1941.

15. Foulds, G. S.: An Unusual Kidney Tumor: Malignant Papillary Cystadenoma and Papillary Carcinoma with Clear Cells, *Tr. Am. A. Genito-Urin. Surgeons* **34**:9-13, 1941.

16. Cahill, G. F., and Fish, G. W.: Surgical Aspects of Polycystic Kidney Disease, *Tr. Am. A. Genito-Urin. Surgeons* **34**:81-87, 1941.

distress and failing renal function, are due to factors not directly attributable to the disease itself, the prognosis is excellent. The results, of surgical intervention are promising, often even dramatic, and the end results are of long duration.

The surgical procedures carried out in this group of cases were nephrectomy in 6 cases, incision and drainage of cysts in 14 and incision and drainage of perinephritic abscesses in 3 cases.

Two deaths followed operation; 1 death occurred two hours after operation, from shock, and 1 occurred fifty days after operation, from bilateral renal infection.

Follow-up data concerning the patients operated on are summarized as follows: Seventeen patients were alive and symptom free from one to sixteen years after operation; 2 patients died from renal failure three years after operation; 1 patient died from the same cause six years after operation, and 1 patient died seven years after operation.

Doolin¹⁷ reports that death from uremia occurred in a case of polycystic kidney. In estimating the cause of the patient's death, Doolin concludes that the absorption of the extravasated proteins from the blood in a hematoma and in torn muscle and their subsequent excretion by the kidneys made too great a physiologic strain for these organs, which hitherto had responded without protest to the various strains which an active outdoor life had laid on them.

Polycystic kidney is divided into two types: One is the congenital type in which the persons who have it either are stillborn or die shortly after birth; the second afflicts adult persons and does not cause symptoms until after the twentieth year. Renal failure in the presence of the second type progresses slowly with long periods of survival.

Trauma.—Cheetham¹⁸ reported 43 cases of severe trauma to the kidney. Twelve of the patients were treated medically; the condition of 9 was acute, and the condition of 3 was of the type illustrating the late effects of renal injury. In 31 cases operation was performed. In 5 of these relief was obtained by conservative surgical treatment. All the cases were of the type in which late complications of renal trauma are presented. Nephrectomy was necessary in 26 cases: in 9, because of the acute symptoms which followed immediate trauma and in 17, in which the condition was of the late type, because of a complicated aftermath. In the total of 43 patients treated there were no deaths.

17. Doolin, W.: An Unusual Fatality from Uraemia, *Brit. J. Surg.* **28**:500-502 (Jan.) 1941.

18. Cheetham, J. G.: The Clinical Management of Renal Trauma: Collective Review, *Surg., Gynec. & Obst.* **72**:573-584 (June) 1941.

Gunshot Wounds.—Scholl¹⁹ states that gunshot wounds of the kidney are usually secondary in importance to injuries of the adjacent viscera. In most cases, the situation of the wounds and the presence of hematuria are the first indications of renal damage. Hematuria is usually present, but the content of blood in the urine usually is not excessive in the majority of cases. In the early stages, hematuria tends to cease spontaneously after several days. Secondary hemorrhage into the bladder is fairly frequent. Cystoscopy and excretory urography are of little diagnostic aid in the presence of acute injuries. The immediate question to be settled is whether or not operative intervention is imperative. Physical observations, wound of entry, pain, swelling and hematuria generally determine the diagnosis and the situation of the lesion.

There are three possible surgical procedures in the care of wounds of the kidney. The first is drainage of the renal area, which permits inspection, evacuation of blood clots and control of bleeding. This is the most satisfactory procedure in most cases and is attended by the lowest mortality rate.

The second is composed of partial nephrectomy, renal repair and plastic operations, but these are not satisfactory in the case of open wounds. Partial procedures do not remove the cause of the bleeding and are rarely justifiable.

The third is nephrectomy, which may be necessary in some cases of persistent hematuria or in the presence of multiple lacerations of the parenchyma. It removes a potential field for infection and limits future bleeding from the operative site. Nevertheless, it is a difficult and hazardous procedure in the early days after injury, and most observers agree that only in rare cases is it indicated or advisable.

Pyelonephritis.—In a series of 72 patients reported on by Prather,²⁰ recurrent pyelonephritis of pregnancy appeared to have an incidence of 23 per cent. The incidence is definitely increased if the urine remains infected during the interval between pregnancies. If the urine becomes sterile during the interval between pregnancies, the chance of recurrent pyelonephritis becomes less than 1 in 5, whereas if the urine remains infected the ratio becomes 1 in 2. There appears to be no tendency toward hypertension during a succeeding pregnancy as the result of pyelonephritis during a previous pregnancy.

19. Scholl, A. J.: Gunshot Wounds of the Kidney, Tr. Am. A. Genito-Urin. Surgeons **34**:65-73, 1941.

20. Prather, G. C.: Recurrent Pyelonephritis During Pregnancy, Tr. Am. A. Genito-Urin. Surgeons **34**:45-50, 1941.

Harrison and Bailey²¹ state that asymptomatic urinary infections are much more frequent among patients who have diabetes than among those who do not. Asymptomatic urinary infections in the diabetic state may lead to serious lesions of the kidneys. Necrosis of renal tissue extends rapidly, once the infection gains a foothold. It is increased in some cases by centripetal propagation of thrombi which form about the areas of infection. A consideration of the end results of infection of the urinary tract among patients who have diabetes emphasizes the importance of treatment of the infection before irreplaceable tissues have been destroyed.

Perinephritis.—Toulson²² states that perinephritic abscesses practically always are associated with pathologic conditions of some form in the kidney. The initiating lesion may be caused by an infection arising from the cortex alone or from pyonephrosis.

In Toulson's series of 41 cases of perinephritic abscess, an analysis was made to determine how many patients had demonstrable lesions of the kidney.

The anatomic characteristics of the perirenal tissues and the exposure of these tissues to renal infections make it seem that all perinephritic abscesses are secondary. Adhesions between the capsule of the kidney and the perinephritic tissues, a common operative finding, would lead to the belief that perinephritis, although it is not regularly diagnosed, is rather common.

In only 13 of this series of 41 cases could pyonephrosis or a destructive renal lesion be demonstrated. In 27 cases, the lesions were proved or assumed to have metastatic origin; in 1 case the lesion was caused by direct extension of tissue.

The onset of the symptoms varied in time from twenty-four hours to four weeks before admission of the patient to the hospital, the average being between ten days and two weeks. Chills, fevers, sweats, renal pain and other symptoms were accompanied by prostration, bulging of the loin and costovertebral tenderness and were present in practically all the patients. Those patients who had destructive renal lesions invariably had an elevation of the nonprotein nitrogen in the blood.

In most of the cases there was a definite roentgen finding of a mass on the affected side, concavity of the spinal column, obliteration of the shadow of the psoas muscle, elevation of the diaphragm and displacement of the colon and the ureter.

21. Harrison, J. H., and Bailey, O. T.: The Significance of Necrotizing Pyelonephritis in Diabetes Mellitus, J. A. M. A. **118**:15-20 (Jan. 3) 1942.

22. Toulson, W. H.: Perinephritis and Perinephritic Abscesses, Tr. Am. A. Genito-Urin. Surgeons **34**:41-44, 1941.

Incision and drainage were all that was necessary to effect cure in practically all cases in which the condition was of metastatic origin. It was considered unwise to break up the walls of a well circumscribed abscess in order to try to deliver the kidney.

Nephrectomy was done in 5 cases in which perinephritic abscess was complicated by renal destructive lesions, and other renal operations were performed in the remaining 8 cases of this character. This was done even though a second operation was necessary.

Renal Hypertension.—Ravich²³ states that hypertension can be caused by increased peripheral resistance and ischemia within the kidney due to generalized toxic effects on the intrarenal circulation, such as occurs in cases of various types of nephritis. It may result also from mechanical compressive forces at or near the hilus of the kidney, producing renal ischemia, augmented back pressure against the general circulation and increased heart action.

The kidney in a normal adult person has been provided by nature with an extrarenal pelvis and a wide hilus. These act as efficient shock absorbers against renal ischemia and hypertension. A certain proportion of human beings, not so fortunate, are afflicted with a persistent fetal type of kidney, with its intrarenal pelvis and narrow hilus. Although in the lower animals this kind of kidney is not much of a handicap, in man, with his erect posture, such organs are vulnerable to various stresses and strains that lead to renal ischemia and hypertension. Because of the restricted space in the hilus of these intrarenal pelvic kidneys, even minor pathologic forces can do considerable harm. The increased mobility of the human kidney, due to the open inferior end of its fatty capsule, has an important influence on the patency of the large renal vessels at the hilus.

The renal circulation, which comprises a third of the entire blood volume, when impeded by the cramped hilus of an intrarenal pelvis creates a traffic jam within the blood stream as certain in its effects as that of a bottle neck on a highway. The resulting back pressure, Ravich says, increases the burden on the heart and results in hypertension.

In a series of 200 cases, Ravich was impressed by the regularity with which hypertension was accompanied by disease in intrarenal types of kidney pelvises. On the other hand, because of the cushioning effect inherent in the extrarenal type, essential hypertension in such protected kidneys appeared extremely unlikely, even though the existing pathologic changes were of considerable degree.

23. Ravich, A.: Hypertension: A New Clinical Concept of Its Etiology, *J. Urol.* **46**:641-658 (Oct.) 1941.

Since essential hypertension may exist for a long time without apparent impairment of renal function, the status of the kidney and its circulation as the source of the trouble is unfortunately usually overlooked. Careful interpretation and recognition of even mild abnormalities ascertainable by the making of so-called intravenous pyelograms are essential for early diagnosis and prophylaxis.

On the basis of examination of intravenous urograms, the physician should be able to make a long range forecast of hypertensive possibilities among patients who have intrarenal pelvic kidneys. This should be particularly interesting to statisticians of insurance companies in their studies of life expectancy and its relation to renal diseases. By recourse to the huge actuarial statistics maintained by these companies, it should be relatively simple for them to ascertain in what proportion, if any, of patients with extrarenal pelvic kidneys hypertension ever develops.

Allen²⁴ states that the typical effect of clamping or ligation of explanted kidneys is one of acute hypertension which persists throughout the period of asphyxia. This acute hypertension occurs also from asphyxia of only one kidney. It can be superimposed on existing chronic hypertension. Restoration of circulation is followed by a rapid decrease to the original pressure or even to a lower pressure.

The nervous character of this type of hypertension is evident from its occurrence during a time in which humoral factors from the kidney are excluded.

The nervous mechanism concerned in hypertension was investigated only to the extent of experiments carried out with the aid of general and local anesthesia. A psychic component is evidenced by the higher pressures of nervous excitable dogs when compared with the lower pressures of quiet passive ones. A definite although less marked hypertension still occurs when the psychic factor seems to be eliminated by anesthesia. The most probable interpretation of the available facts points to a nervous reflex element in the hypertension, which occurs as long as a reflex response is possible.

When renal asphyxia is continued for a period beyond any possible physiologic limits (e. g., six hours), rather brief secondary hypertension may ensue. Apparently this result does not occur except when the asphyxia of both kidneys or of one kidney has been so prolonged that it causes rapidly fatal intoxication. Possibly, therefore, any toxic asphyxial products noted in experiments of this type may be of post-mortem character, so to speak, and not representative of anything occurring physiologically or clinically.

24. Allen, F. M.: Acute Hypertension with Clamping or Ligation of Explanted Kidneys, *J. Urol.* **46**:834-852 (Nov.) 1941.

Results of the experiments with explanted kidneys, although involving complex factors, illustrate the complex control of blood pressure in the intact organism. Within time limits which reasonably can be considered physiologic (e. g., two to four hours), hypertension arising from substances supposedly produced during renal asphyxia either is nonexistent or is nullified by the predominant nervous control. Therefore, without denial of the reality or the value of the observations made under nonphysiologic conditions, warning should be given against attempts to expand what might be called artificial findings into a universal theory of hypertension.

Prinzmetal, Hiatt and Tragerman²⁵ reported a case of hypertension in which the patient had bilateral renal infarction. A woman 53 years old suffering from chronic rheumatic heart disease became hypertensive within the space of a few days after an acute attack of severe abdominal pain. Elevation of blood pressure was accompanied by increasing suppression of urine short of complete anuria and by progressive retention of nitrogen, and death occurred in the presence of uremia. At necropsy there were found occlusion of both main renal arteries by thrombus formation, probably of embolic origin, and almost complete infarction of both kidneys. Since the train of events was identical to that occurring in the experimental production of hypertension, this case offered a perfect example in a human being of hypertension resulting from acute renal ischemia.

Perfusates that were prepared immediately after death from one of the infarcted kidneys revealed the presence of a pressor substance which presumably is the same as that responsible for the hypertension that follows termination of complete renal ischemia in experiments on animals. Attention is called to hypertension as a neglected sign in occasional instances of renal infarction.

URETER

Transplantation.—Hinman and Weyrauch²⁶ state that the end of the implanted ureter constitutes an area of crucial importance in determination of the success or failure of ureterointestinal anastomosis. They carefully traced the pathologic changes which occur in this structure, especially with a view to demonstration of the hazards which accompany damage to the blood supply and the entrance of infection; if it extends above the site of the anastomosis, either anemic necrosis or infectious

25. Prinzmetal, M.; Hiatt, N., and Tragerman, L. J.: Hypertension in a Patient with Bilateral Renal Infarction: Clinical Confirmation of Experiments in Animals, *J. A. M. A.* **118**:44-46 (Jan. 3) 1942.

26. Hinman, F., and Weyrauch, H. M.: An Experimental Study of Uretero-Intestinal Implantation: V. The Destiny of the Implanted Ureter, *Surg., Gynec. & Obst.* **74**:129-136 (Feb. 1) 1942.

gangrene gives rise to fatal peritonitis. A virulent infection in the ureteral stump causes serious damage to the upper part of the urinary tract, first by acute ureteritis with its attendant stasis and later by the formation of stricture. The changes in the end of the ureter, therefore, play a great part in accounting for the morbidity and the mortality, both early and late, which attend the operation.

Colby²⁷ reports 10 cases of renal tuberculosis in which the ureters were transplanted to the skin. Advanced disease was present in all. In many there were genital lesions, active tuberculosis of bones and probably other areas of unsuspected disease, although there were no active pulmonary lesions. The operation of cutaneous ureterostomy entails little risk. No deaths resulted directly from the operation, although 1 patient died from a ruptured tuberculous ulcer of the small intestine before leaving the hospital. Simultaneous bilateral ureterostomy was done for 2 patients who had tuberculosis of both kidneys. Both died within a few months and neither was particularly benefited while alive. Considerable benefit from the operation was obtained for those patients whose remaining kidney was diseased after removal of the opposite tuberculous kidney. Their intolerable vesical symptoms were relieved, and the progress of renal damage was lessened. Five such patients, who had undergone ureterostomy, were alive and useful at the time of Colby's report. If the operative result is a rosette of ureteral mucous membrane which projects beyond the skin, there is reason to believe that patients can live comfortably without the need of catheters and that they can escape the formation of stricture at the skin, even in the presence of active renal tuberculosis. If this is true, these patients can easily care for themselves without the nuisance of changing of catheters, and the danger of pyelonephritis, secondary infections with urea-splitting bacteria and formation of stones is lessened. Transplantation of ureters to the skin, as usually performed, holds no guarantee of a satisfactory junction of skin and ureter. A simple method which may help to accomplish this is suggested. Cutaneous ureterostomy is the most effective method for relief of symptoms from the hopelessly infected tuberculous bladder.

Goldstein²⁸ reports 8 cases of ureterocutaneous transplantation. In 5 of the 7 cases in which a tumor was present, the carcinomatous bladder was allowed to remain, with no intention of removal of it because of the advanced stage of the carcinoma and the poor condition of the patient.

27. Colby, F. H.: Cutaneous Ureterostomy in Active Renal Tuberculosis, *Tr. Am. A. Genito-Urin. Surgeons* **34**:101-114, 1941.

28. Goldstein, A. E.: Ureterocutaneous Transplantations, *J. Urol.* **46**:873-884 (Nov.) 1941.

The operation is simple and is applicable to all poor risk patients who have carcinoma of the bladder, when suffering is excruciating and all other measures have failed. The operation is applicable also to all patients who have diseased infected kidneys with dilated ureters, especially in association with carcinoma of the bladder. Three patients died within ten days after the operation. Three patients lived comfortably from eight to ten months after the operation. Two patients were still alive and comfortable thirteen and thirty months, respectively, after the operation.

In discussing ureteroenterostomy, Smith²⁹ states that the transplantation of normal ureters which drain uninfected kidneys does not constitute too great a risk to make the procedure prohibitive. Late results, especially among older people, are not too good. In the majority of patients in Smith's series of cases, one kidney at least showed evidences of faulty drainage. Calculi developed among 4 patients. Several patients had elevated values for nonprotein nitrogen—evidence of bilateral renal insufficiency.

Infection and dilatation of the upper part of the urinary tract which so commonly accompany carcinoma of the bladder constitute a definite hazard and warrant transplantation of the ureters to the skin rather than to the bowel.

The clearest indication for ureteroenterostomy is exstrophy of the bladder; incurable vesicovaginal fistula, unless it is accompanied by radiation changes and urinary infection, is also a valid reason for this operation.

Poth³⁰ discusses implantation of the ureters into the rectosigmoid and reviews the postoperative course of patients who underwent the procedure. His operation of implantation of the ureters is divided into two stages; in the first stage, the ureter is embedded in the wall of the bowel without interruption or diversion of the urinary stream, and in the second stage, the opening is made between the ureter and the bowel, with diversion of the urinary stream into the intestine. At the first operation, the ureter is freed, the serosa of the rectosigmoid is split, the ureter is placed in the opening left by the serosa, and the serosa is covered over the ureter. At the next procedure, the partition between the ureter and the sigmoid is cut away by an ingenious device consisting of a cutting wire assembly. The lower end of the distal segment of the ureter is then cut off and inverted into the bowel.

29. Smith, G. G.: Indications for Uretero-Enterostomy, *Tr. Am. A. Genito-Urin. Surgeons* **34**:93-99, 1941.

30. Poth, E. J.: Implantation of Ureters into the Rectosigmoid with a Study of the Postoperative Course, *Surg., Gynec. & Obst.* **74**:221-226 (Feb.) 1942.

Obstruction.—Creevy³¹ states that noncalculous obstruction at the ureteropelvic junction is usually caused by stricture, by distortion, by peripelvic fascia or by neurogenic dysfunction.

A plastic operation is indicated when the kidney contains enough normal tissue to sustain the life of the patient. It is especially indicated for young persons and for those who have bilateral lesions. Creevy says that the most satisfactory operation for this condition is what he calls the Y plasty of Schwyzer and Foley.

Creevy reports 5 examples of uncommon types of obstruction, including 1 case of granuloma and 3 of polyps of the mucosa at the junction, and 1 instance of obstruction of the pelvis itself by accessory vessels after Y plasty. Four patients were treated by Y plasty and 1 by excision of the redundant pelvis and reimplantation of the ureter.

The occurrence of polyps contraindicates any operation which does not include careful exploration of the mucosa of the ureteropelvic junction. When accessory vessels cross the ureteropelvic junction, they should be excised even though a plastic procedure may leave them well above the junction, since they may later embed themselves in the pelvis and reproduce obstruction.

Pyoureter.—Davison³² reported a case in which pyoureter and periureteritis occurred seventeen years after nephrectomy for calculous pyonephrosis. The stump of the ureter contained a calculus. No genitourinary or other symptoms referable to the process had been present during these seventeen years. Surgical removal was carried out successfully.

Davison states that it is important to determine at the time of nephrectomy whether or not the ureteral orifice in the bladder will remain patent. If because of the presence of a calculus or stricture, free drainage into the bladder is prevented, complete ureterectomy should be carried out to obviate future infection and empyema in the ureteral stump.

Stricture.—Spastic ureteritis³³ is a clinical entity which is similar in symptomatologic aspects to true organic stricture of the ureter but which can be distinguished from it by the prompt relief afforded by simple dilation. The condition should be suspected among all patients, particularly women, who present symptoms of vague abdominal pain, asso-

31. Creevy, C. D.: Unusual Types of Obstruction at the Ureteropelvic Junction. *Tr. Am. A. Genito-Urin. Surgeons* **34**:115-122, 1941.

32. Davison, S.: Pyoureter Seventeen Years After Nephrectomy, *J. A. M. A.* **118**:137-138 (Jan. 10) 1942.

33. Walther, H. W. E., and Willoughby, R. M.: Spastic Ureteritis (Ureteral Stricture): Essential Clinical Considerations, *J. Urol.* **46**:671-683 (Oct.) 1941.

ciated with varying degrees of urinary disturbance, not demonstrably due to disease in some other organ.

Dilation of the ureter, repeated as necessary, relieves most patients promptly. In the occasional case, surgical intervention may prove to be necessary.

It is now rather generally recognized by urologists that there is such a thing as painful stenosis or a spastic condition of the ureter. Opinions differ as to its frequency and its causation. There is little difference of opinion, however, as to the clinical picture, regardless of the causative factors, and there is a rather general belief in the efficacy of ureteral dilation as a means of relief from it.

Stone.—Finney³¹ discusses the principle of the application of traction in the treatment of ureterolithiasis. His technic is simple. In all but 5 of 50 cases, the stone was removed with a homemade instrument, so to speak, constructed as follows: A no. 6 French x-ray catheter with either a whistle tip or a taper tip is modified by the insertion of a silk suture in the distal end, care being taken to tie the knot so that it becomes as small as possible. A wire stylet should be inserted to stiffen the catheter, which at this stage is ready for use. The catheter, with thread attached, is passed transvesically to the stone and beyond it, if possible. If the catheter will not pass, a local anesthetic agent is injected, and afterward a few drops of liquid petrolatum are utilized for lubrication. In nearly every instance, the catheter will then pass with little difficulty.

The thread-bearing catheter is moved onward until the renal pelvis is reached. At this point the stylet is withdrawn a few inches, and the cystoscope is removed; the catheter is left in place. By pushing toward the kidney with the catheter and pulling away from it with the suture, the urologist can make a loop without difficulty or injury. There is plenty of room in the dilated renal pelvis. Once the loop has been made, thread and catheter are pulled down the ureter together, until the stone is engaged in the loop. No doubt will be experienced as to when this occurs, since firm resistance is encountered.

The urologist is now in a position to exert as much traction as he wishes on the stone, for the loop rarely slips. It is best not to use traction greater than 1 or 2 pounds (0.5 to 0.9 Kg.), and an attempt should never be made to remove the stone immediately. A small scale is attached to the end of the catheter; the patient is put to bed, and pain is controlled by administration of an opiate. The nurse is instructed to exert traction of 2 pounds (0.9 Kg.) on the scale and to maintain it for a moment, every hour or two, for twenty-four hours. At the end

34. Finney, R. P.: The Principle of Traction in the Treatment of Ureterolithiasis, J. A. M. A. **117**:2129-2131 (Dec. 20) 1941.

of that time, the patient is anesthetized lightly with gas, and traction up to 5 pounds (2.3 Kg.) is exerted.

In Finney's series of 50 cases, the stone was obtained at the end of twenty-four hours in 47. Treatment was continued in the 3 cases in which calculi were refractory to the procedure and was successful in 2, in which the stone was passed within thirty-four and forty-two hours, respectively. The treatment in the third case was a failure. Having kept the loop in place for seventy-two hours without budging the calculus, Finney removed the calculus by open operation.

Livermore³⁵ sounds a note of warning concerning intraureteral manipulation. Pointing out that he himself devised an instrument for dislodgment of ureteral stones, he condemns all metal instruments for promoting the removal of stones in the ureter. The ureter is easily damaged, he says, and since the introduction of American catheters, which are much stiffer than the ordinary catheter that has been used, puncture of the ureter is becoming much more frequent. He states that Heckel recently reported 15 cases in which the ureter had been punctured. After an experience of thirty years in urologic practice, Livermore encountered his first puncture of a ureter while he was using one of the stiff catheters in question. The patient had a stone in the ureter, and an attempt was being made to pass the catheter beyond it. He suggests that the pressure of a stone might produce spots of necrosis or chronic inflammatory reactions, and hence, if his suggestion is valid, the ureter would be much more susceptible to damage than otherwise.

Bumpus³⁶ states that in the manipulation of ureteral stones the condition confronting the urologist is urinary obstruction associated with infection, a combination that can result in the most serious of consequences. He emphasizes the dangers of infection in the presence of obstruction. Severe febrile reaction under these circumstances is likely to occur rapidly as a result of renal involvement, and septicemia not infrequently follows. For this reason, it seems imperative that the urologist inform the patient of these dangers before he attempts manipulation and obtain permission of the patient to resort to surgical removal of the stone immediately if such untoward symptoms develop.

BLADDER

Tumor.—Young³⁷ discusses intravesical resection of the wall of the bladder and the peritoneal coat for certain tumors of the bladder and

35. Livermore, G. R., in discussion on Finney.³⁴

36. Bumpus, H. C., Jr., in discussion on Finney.³⁴

37. Young, H. H.: Intravesical Resection of the Bladder Wall and Peritoneal Coat for Certain Bladder Tumors, *Tr. Am. A. Genito-Urin. Surgeons* **34**:183-189, 1941.

reports a case. The operation is an extension of the technic of transvesical radical removal of tumors of the bladder together with a large portion of the wall of the bladder and the peritoneum covering it, and it appears to be the ideal method for radical removal of tumors in that region. For tumors which extend down the ureter and invade the bladder, as was the situation in the case described by Young, extension of the transvesical peritoneal technic is shown to be easy.

Young stresses the importance of removal of the peritoneum covering the wall of the bladder in resection for tumor of the posterior wall. It has been shown to be possible to operate entirely intravesically, without first entering the peritoneal cavity, after a wide suprapubic incision has been made in the midline and after insertion of a four-bladed, self-retaining retractor. This provides such wide exposure of the bladder that it is easy to pick up the mucosa at points distant from the tumor and to excise the entire wall of the bladder with its peritoneal coat and to close the defect extraperitoneally through the bladder. In the case reported in detail, it also has been shown that this same technic can be employed effectively for removal of a ureteral tumor which has grown into the bladder.

Colby³⁸ states that at the Collis P. Huntington Memorial Hospital, in Boston, work has been carried on for about four years with the supervoltage unit. He and his associates there have tried not to be overenthusiastic about the treatment of tumors of the bladder by supervoltage radiation and have carefully guarded against creating any impression that such a procedure might be curative in its effects on tumors of the bladder.

The communications of Colby and associates in the past have shown that among approximately 50 per cent of the patients treated adequately with supervoltage radiation, the tumors have definitely regressed, i. e., the tumors have been reduced to approximately a third or a half of their original size. Among about 33 per cent of the patients, the tumors have at one time or another actually disappeared completely, as far as could be determined by cystoscopic examination. This, however, was not by any means regarded as signifying cure.

At the time of their writing (1941), Colby and associates had approximately 70 patients who were adequately treated and whose course thereafter was carefully followed. Among about 50 per cent of the patients, well marked regression of the tumors occurred, and among about a third of the patients, actual disappearance of the tumors was

38. Colby, F. H., in discussion on papers of Barringer, Nesbit and Cummings,⁴⁷ Hamer and Wishard⁵⁸ and Wishard,⁵⁹ *Tr. Am. A. Genito-Urin. Surgeons* **34**:272-273, 1941.

noted. In many instances, the tumors eventually recurred. Among only a few of the patients the tumors remained absent from the bladder for periods long enough to afford any hope that certain tumors might be cured by external radiation. Colby considers such a possibility doubtful. On the other hand, he says, the observer cannot but gain the impression that if a little more could be added to treatment by external radiation, some of these tumors might be eradicated. He says that is what he and his associates were trying to do during the year prior to the time of his report.

He states that patients receive a preliminary course of external radiation, which usually is 8,400 r. If at the end of three weeks there has been a noticeable well marked regression of the tumor, then interstitial radiation by the implantation of gold radon seeds is added to the procedure, before the tumor has had an opportunity to receive the effect of the external radiation. Then, if the situation warrants it, the patient receives another 2,800 or 3,600 r of external radiation.

Tumors of the bladder will regress in entirely different ways, Colby reports. Regression is usually expected to take place within four or five weeks. This, however, is not true of all tumors, a fact that is well illustrated by the course of 1 patient who about a year prior to the time of Colby's report received a preliminary course of external radiation for an epidermoid carcinoma about 3 cm. in diameter, situated on the floor of the bladder. The tumor did not regress under radiation after the first course, and the patient received a second course, which amounted to a total of 12,000 r—a good preliminary course of radiation. Again there was no evidence that the tumor was regressing. Total cystectomy, with ureteral transplantation, was carried out, and the patient died in about ten days of an infection of the blood stream. At necropsy it was seen that the tumor had regressed to a diameter of only about 1 cm., and study of histologic sections disclosed only small nests of active tumor cells, with much fibrosis. In other words, the tumor, in the meantime, had undergone such marked regression that Colby thinks that he and his associates were not justified in attempting any such radical procedure as total cystectomy. If some type of interstitial radiation had been added to the treatment of this patient, Colby says, the patient would have had a much better chance of recovery.

Amyloidosis.—Rusche and Bacon³⁹ report 2 cases of amyloidosis of the urinary bladder, each substantiated by adequate proof of the pathologic lesion.

39. Rusche, C. F., and Bacon, S. K.: Solitary Tumor-Like Amyloidosis of the Urinary Bladder, *Tr. Am. A. Genito-Urin. Surgeons* 34:163-168, 1941.

After a review of the literature, Rusche and Bacon conclude that solitary tumor of amyloid in the urinary bladder is one of the rarest pathologic lesions. Clinically, they state, this lesion is confused with neoplasm; however, it can be readily identified by means of special stains for amyloid. The literature contains 3 cases of amyloidosis of the urinary bladder, 4 cases of amyloidosis of the urethra and 1 case each of amyloidosis of the renal pelvis, the seminal vesicle and the wall of the ureter.

Interstitial Cystitis.—Pool and Crenshaw⁴⁰ report on 34 patients who had interstitial cystitis treated by means of irrigation with silver nitrate in solution. They give a preliminary review of their results. At the time of their report, none of the patients had failed completely to respond to this therapy, except those concerning whom the diagnosis of interstitial cystitis was not definite. In other words, all except 1 of those patients whose condition was typical made satisfactory progress. This 1 patient had improved and was without pain but still continued to have moderate frequency of urination when last seen. Pool and Crenshaw emphasize the fact that they cannot state positively that any of their patients were cured, although their symptoms were relieved.

Their method of procedure is different from that advocated by other authors. Other physicians employ strong solutions immediately and then rely on local anesthesia or sedative agents for control of the pain which is caused when a 0.25 or 0.5 per cent solution of silver nitrate is used. Crenshaw and Pool prefer to begin the treatment with a dilute solution (1:5,000) and to increase the strength daily until a solution of 1 per cent has been reached. When the stronger solutions are used, the bladder is thoroughly lavaged with the solution each time, and then 2 fluidounces (59 cc.) of the solution is allowed to remain in the bladder for five minutes. At the end of this time, the bladder is emptied by means of a catheter.

Hunner's Ulcer.—Kreutzmann⁴¹ discusses the treatment of Hunner's ulcer with roentgen therapy. A group made up of 5 women and 1 man received deep roentgen therapy over the region of the bladder in doses varying from 1,200 to 4,200 r. No change was noted in the man or in 2 of the women. In 3 of the women there was complete relief of symptoms with disappearance of the ulcer for periods ranging from seven to twelve months. In no case was permanent cure obtained. The

40. Pool, T. L., and Crenshaw, J. L.: Treatment of Interstitial Cystitis with Silver Nitrate, Proc. Staff Meet., Mayo Clin. **16**:718-720 (Nov. 5) 1941.

41. Kreutzmann, H. A. R.: The Treatment of Hunner's Ulcer with Deep X-Ray Therapy, J. Urol. **46**:907-912 (Nov.) 1941.

disadvantages of this form of therapy are the limitation of dose and the production of the menopause in women.

Simple Ulcer.—Boyd⁴² states that ulcers of the bladder other than those resulting from cancer, syphilis, trauma and radiotherapy have been reported, but not often, in the literature. The terms employed to distinguish these ulcers have been varied. They have been called "simple chronic ulcer," "perforating ulcer," "the ulcer of interstitial cystitis" and "incrusting ulcer." To the ulcers designated by these terms is added an ulcer caused by staphylococcal infection of the bladder.

The causative factors mentioned have been trophic changes in the wall of the bladder, metastatic infection of the mucosa or the submucosa, obliteration of some of the small blood vessels of the mucosa by various processes and infection of the bladder by staphylococci and other organisms.

Schulte reported an ulcer of the bladder much like the one recorded by Boyd. It seemed to be caused by a strain of staphylococci which in experiments with the inoculation of animals had a definite tendency to produce lesions of the urinary tract rather than lesions elsewhere. In 1 animal, this strain produced an ulcer of the bladder like the one found in the patient.

In Boyd's case, the patient was a young man of 20 years who for five years before the ulcer appeared had had increased arterial tension, orthostatic albuminuria and general malaise. Eighteen months earlier, bilateral hydronephrosis had been found, but the bladder was normal. Six months later, the bladder was infected by staphylococci and *Streptococcus faecalis*, but no urinary symptoms were present. Severe bleeding persisted for ten days after cystoscopy, but the ulcer was not seen. About ten months later, an ulcer was found on the posterior wall of the bladder, where the wall protruded to overlie the region of the ureteral ridge. This protrusion was more or less fixed. The ulcer was about 5 cm. in diameter; it was shaggy, had a red base and fairly well defined edges and was elected a little above the surrounding mucosa. The ulcer was excised.

Postpartum Studies.—In a series of 116 cystoscopic examinations of the bladders of women in the postpartum period, Bennetts and Judd⁴³ found general relaxation and minor degrees of mucosal edema. Ecchymosis of the mucosa of the bladder was present to a minor degree in 12

42. Boyd, M. L.: Ulcers of the Bladder: The Report of a Case of Unusual Ulcer of the Bladder of Unexplained Origin, *Tr. Am. A. Genito-Urin. Surgeons* 34:145-161, 1941.

43. Bennetts, F. A., and Judd, G. E.: Studies of the Post-Partum Bladder, *Am. J. Obst. & Gynec.* 42:419-427 (Sept.) 1941.

per cent of the cases and to a moderate degree in 4.3 per cent of the cases. The prevalence of these conditions was not increased by breech extraction nor were the conditions seen in 2 cases in which delivery was achieved by the midforceps operation, 1 case in which the procedure was version and extraction and 1 case in which low cervical cesarean section was done. Cystometric studies revealed hypotonic bladders with decreased bladder sensation and increased capacity in 86.2 per cent of the entire series. Type of delivery, trauma and the use of analgesia prior to delivery do not explain this dysfunction.

Fistula.—Ewell and Jackson⁴⁴ discuss vesicointestinal fistula, stating that it may occur among persons of any age but that it is more common among those between the ages of 40 and 70 years. Among infants and young children, it is practically always congenital in origin. It is approximately three times more common among men than among women, probably because of the presence and the position of the uterus and because of the less frequent occurrence of diverticulitis of the sigmoid among women. In Ewell and Jackson's series of 11 cases, the youngest patient was 26 years old and the oldest 72.

The causative factors of vesicointestinal fistula are: (1) congenital, usually associated with anal anomalies, (2) traumatic, of which surgical procedures account for approximately half, gunshot wounds being the next most common cause, (3) inflammatory, in which group diverticulitis of the sigmoid is the most common and (4) neoplastic. In the fourth type, in which are included the causes of approximately 20 per cent of all cases, carcinoma of the rectum, carcinoma of the sigmoid and carcinoma of the bladder are most common and occur in the order named.

Fistulas between the rectum and the bladder and between the sigmoid and the bladder may occur in about equal numbers.

The fistula is a direct passage when it is due to a neoplasm; when it is secondary to inflammatory disease, it nearly always develops after the formation of a localized abscess and is usually a tortuous tract.

The symptoms in a given group of patients are variable. In those cases in which the fistula is due to diverticulitis of the sigmoid, the onset is generally gradual, with repeated attacks of tenderness and pain in the lower left part of the abdomen and cramps due to the diverticulitis. These attacks may be accompanied by recurrent attacks of cystitis. Pneumaturia and the passage of feces per urethram are usually spoken of as being pathognomonic of vesicointestinal fistula. Certainly this is true of the passage of fecal matter. The passage of urine per rectum is another cardinal and frequent symptom of vesicointestinal fistula.

44. Ewell, G. H., and Jackson, J. A.: Vesico-Intestinal Fistula, *J. Urol.* 46:693-698 (Oct.) 1941.

In a few cases, the history alone will be a sufficient basis for a diagnosis. Cystoscopy, excretory urography, the making of cystograms, gastrointestinal studies carried out with the aid of roentgenograms and proctoscopic examinations all should be done. Of these, cystoscopy is probably the most valuable. In a few cases, an unsuspected fistulous opening in the bladder has been found at cystoscopy. Frequently, the opening in the bladder is not seen, being obscured by an ulcerated or granulomatous area. Probing of the area with an x-ray ureteral catheter should be done cautiously to avoid creation of a fistula. Bubbles of gas or fecal matter extruding into the bladder may be observed.

In most cases, a surgical procedure of some type is required. The importance of performance of preliminary colostomy, of a type that will result in prevention of spilling of the fecal current from the upper segment into the lower segment of the colon, and the allowance of adequate time for the inflammatory reaction to subside, cannot be over-emphasized. Colostomy should be carried out as close to the fistula as possible, so that a redundant loop of bowel above will not remain.

Because of the nature of the lesions which cause vesicointestinal fistula, the prognosis usually is grave, and the necessity for multiple operations creates a high operative mortality rate. Spontaneous healing rarely occurs in these cases. In the traumatic and postoperative types, a more favorable outcome may be anticipated. In a small percentage of cases, the lesion may heal spontaneously. In the remainder the condition usually is amenable to surgical treatment. Recurrence after operation has been reported in a few instances. The literature reveals that approximately a third of the patients are cured.

Irradiation Injury.—Dean and Slaughter⁴⁵ state that the bladder not infrequently is injured by irradiation of the uterus. Although uterine diseases commonly are treated by means of several types of irradiation, the greatest damage to the bladder follows applications of radium. Interstitial fibrosis occurs in the wall of the bladder, and obliterative endarteritis occludes nutrient arteries. Because these changes usually are slow, patients are likely to experience no distress referable to the bladder for a number of years after the uterus has been treated. For this reason, these injuries to the bladder occur almost exclusively among patients cured of the primary uterine disease.

The onset of symptoms is sudden. The patients suffer acutely from frequency of urination, dysuria and hematuria. Cystoscopic examination usually reveals single areas of ulceration surrounded by acute inflam-

45. Dean, A. L., and Slaughter, D. P.: Bladder Injury Subsequent to Irradiation of the Uterus, *J. Urol.* **46**:917-924 (Nov.) 1941.

mation. Both the mode of onset and the cystoscopic picture suggest carcinoma.

Dean and Slaughter have found that sulfanilamide and its derivatives, appropriately chosen on the basis of results of culture of urine obtained from the bladder, produce prompt relief. This is in marked contrast to the unsatisfactory results of previous therapy.

Dean and Slaughter state that it is interesting to note that the symptoms subside as infection is eliminated. Women whose urine is sterile can be rather comfortable, even though ulcerated areas of considerable size persist.

Thompson,⁴⁶ in discussing Dean and Slaughter's paper on injuries to the bladder subsequent to irradiation of the uterus, states that the time of the development of an irradiation injury is important. Many urologists are not aware of the fact that an irradiation injury of the bladder can appear many years after irradiation of the uterine cervix. For this reason, the diagnosis of the lesion is likely to be inaccurate. The urologist will conclude that the process that he sees in the bladder is an extension of the original malignant lesion. A poor prognosis frequently is offered and incorrect treatment is instituted in that further irradiation and sometimes the implantation of radon seeds has been advised in such cases. This leads to further insult of the tissues and ultimately to perforation and a distressing and unnecessary complication. Biopsy of material obtained from the edge of the lesion is desirable. Taking material from the central portion of the lesion will result only in obtaining necrotic fragments of tissue with which the pathologist cannot work. Treatment is important. The main part of the treatment is lavage with the proper solutions and the use of antiseptic agents. Careful curettage of these incrustated ulcers also has been employed, since most of them are incrustated. The urologist must be careful in performing curettage, for the bladder can be perforated easily.

Retention.—Nesbit and Cummings⁴⁷ state that in many cases urinary retention which follows surgical procedures is entirely functional or reflex in origin, since it occurs regularly among patients who are free from organic disease of the urinary tract.

Efforts have been made to prevent as well as to combat postoperative ileus and atony of the bladder by parasympathetic stimulation. Various drugs are known to have this pharmacologic action. There are three

46. Thompson, G. J., in discussion on papers of Dean and Slaughter⁴⁵ and Graves and Guiss, *J. Urol.* **46**:949-950 (Nov.) 1941.

47. Nesbit, R. M., and Cummings, R. H.: The Use of Prostigmine in the Management of Postoperative Urinary Retention, *Tr. Am. A. Genito-Urin. Surgeons* **34**:257-260, 1941.

main groups of parasympathomimetic agents: (1) the choline esters, such as acetylcholine, acetylbetamethylcholine (mecholy) and carbaminoylcholine (doryl); (2) the inhibitors of cholinesterase, such as physostigmine and prostigmine, and (3) the older alkaloids, such as pilocarpine, arecoline and muscarine.

Prostigmine has been recommended because of its low toxicity and because of its alleged proved value.

Gordon, the authors note, reported a series of 85 cases in which prostigmine methylsulfate was used. Fifty of the patients were given a prophylactic dosage before and after operation, the procedure being administration of 1 cc. of a 1:4,000 solution at intervals of two hours, for six doses. Only 2 patients of this group required catheterization. This 4 per cent incidence of atony was compared to an 18.5 per cent incidence of catheterization computed in a control series of 318 cases. Marden and Williamson, the authors state, reported a series of 247 cases in which the patients received prostigmine methylsulfate. Ninety-eight of Marden and Williamson's patients received prophylactic doses of prostigmine methylsulfate; the incidence of postoperative catheterization was 5.1 per cent.

Nesbit and Cummings made observations in a small series of patients treated in the University of Michigan Hospital in an effort to determine the usefulness of prostigmine methylsulfate in the prevention of urinary retention. Patients who had undergone simple appendectomy, herniorrhaphy and anal operations were selected as constituting an ideal group for this study. In a control series of 285 cases, the incidence of postoperative catheterization was 17.5 per cent.

Prostigmine methylsulfate was given in 65 cases. The drug was used in two different ways: (1) as a prophylactic agent and (2) as a therapeutic agent in the treatment of postoperative urinary retention.

The incidence of catheterization was not materially influenced by the prophylactic use of prostigmine methylsulfate in their group of patients.

Prostigmine methylsulfate used as a therapeutic agent for impending retention was given to 13 patients. These patients received 1 cc. of a 1:2,000 solution of prostigmine methylsulfate each hour for four hours, or until the patient voided. Three of the patients (23 per cent) treated in this way required catheterization. The remaining 10 patients voided spontaneously.

In other words, in the clinic in which the authors made their study, in a carefully controlled small series in which prostigmine methylsulfate was given, the value of this drug in materially reducing the expected incidence of catheterization after major surgical procedures was not demonstrated.

Neurogenic Bladder.—Evans,⁴⁸ in discussing the physiologic basis of the neurogenic bladder, states that there are certain practical considerations which should be stressed.

First, the musculature of the bladder should never be allowed to stretch unduly, for if this happens, stretched muscle fibers result, and these fibers, like those of stretched skeletal muscles, are then less well able to respond to nervous activity.

Second, a stretched wall of a bladder is more likely to become infected than one that has not been stretched. Infection followed by fibrosis leads to impairment of vesical function and interferes with the resumption of motor activity when nervous control is restored.

Third, the musculature of the bladder is subject to and can be benefited by passive exercise just as is true of skeletal muscle. Such passive exercise can be accomplished by the employment of tidal drainage.

Nesbit and Gordon⁴⁹ state that autonomous neurogenic bladder results from destructive lesions of the conus terminalis and the cauda equina. Since the internal vesical sphincter shares in the hypertonic process which affects the bladder, it acts as an obstruction to the egress of urine. As with any obstruction of the outlet, decompensation of the bladder and damage to the upper part of the urinary tract ultimately will result if the condition persists sufficiently long. Modern treatment of the autonomous neurogenic bladder attempts to relieve the obstruction of the outlet. Presacral neurectomy has not proved to be satisfactory in Nesbit and Gordon's experience. Transurethral sphincterotomy yields more gratifying results, particularly if it is undertaken before the bladder has become decompensated.

PROSTATE GLAND

Hypertrophy.—Fowler⁵⁰ reports 5 cases in which prostatic obstruction occurred among young adult persons. The youngest was 19 years old; the oldest was 26. They presented in varying degree the characteristic symptoms of prostatism; difficulty in voiding, delay in the start of urination, voiding of a small stream, requirement of a longer time than normal for completion of the act; frequency, urgency and dysuria; overflow incontinence and complete retention. In 3 cases, gross enlargement of the prostate gland was found on rectal examination; in 2,

48. Evans, J. P.: The Physiologic Basis of the Neurogenic Bladder, J. A. M. A. **117**:1927-1930 (Dec. 6) 1941.

49. Nesbit, R. M., and Gordon, W. G.: The Surgical Treatment of the Autonomous Neurogenic Bladder, J. A. M. A. **117**:1935-1936 (Dec. 6) 1941.

50. Fowler, H. A.: Prostatic Obstruction in Young Adults, J. Urol. **47**:16-30 (Jan.) 1942.

the prostate gland was essentially normal in size. The diagnosis was confirmed by cystoscopy in 4 cases. In 1 case, in which the patient was a man 23 years old who had acute retention, it was impossible to reach the bladder with any urethral instrument.

One of Fowler's patients was a man 26 years old for whom fulguration of the obstructing lobe was carried out with a good result. The second patient was a man 23 years old who was treated by the making of multiple incisions from within outward through both lobes; this produced amelioration of his symptoms. This patient and 1 other underwent resection of the prostate gland. The fifth patient was treated by urethral dilation.

Rusche and Bacon⁵¹ report 4 cases in which radical repair of rectourethral fistula was carried out after perineal prostatectomy. Infection caused by *Clostridium welchii* developed in 1 patient after perineal prostatectomy; the patient recovered. In 2 instances, rectal injury was not recognized at the time of perineal prostatectomy. Suprapubic cystostomy is necessary as a preliminary step in the repair of rectourethral fistula. The success of the perineal operation is dependent on complete mobilization of the rectum to a point above the site of the fistula, resection of a cuff of rectum and anastomosis of the rectum to the skin without tension. Section of the rectal sphincter musculature is not indicated.

Emmett⁵² reports a case in which urinary incontinence had been present for fifteen years in a patient with tabes. He says the incontinence was relieved by transurethral resection and states that many patients with vesical dysfunction (heretofore called "cord bladder") can be helped or completely relieved by transurethral resection of the vesical neck. This is especially true of patients who have a neurologic lesion which affects chiefly the sensory nerves, the classic example of which is the patient who is afflicted with tabes dorsalis. A bladder weakened from distention resulting from impairment of the sensory nerves which supply the bladder is more easily obstructed than a normal bladder. Because of this, minimal degrees of obstruction at the neck of the bladder which ordinarily would cause no difficulty may be the cause of vesical dysfunction associated with large quantities of residual urine in the tabetic type of bladder.

The patient, a man of 66 years, had had urinary incontinence for fifteen years. A short time before he was seen, the incontinence had changed to retention, requiring catheterization. The incontinence was

51. Rusche, C. F., and Bacon, S. K.: Recto-Urethral Fistula Following Perineal Prostatectomy: Report of Four Cases, *J. Urol.* **46**:699-706 (Oct.) 1941.

52. Emmett, J. L.: Urinary Incontinence of Fifteen Years' Duration in a Tabetic Patient Relieved by Transurethral Resection: Report of a Case, *Proc. Staff Meet., Mayo Clin.* **16**:728-730 (Nov. 12) 1941.

not a constant dripping of urine but apparently was an involuntary type of urination. Neurologic examination revealed evidence of tabes dorsalis. Cystoscopic examination disclosed moderate relaxation of the vesical sphincter muscles. The urethra in the region of the penoscrotal angle was markedly contracted and would admit only a small resectoscope. This narrowing was the result of large caliber stricture which followed previous urethritis. There was moderate enlargement of all three lobes of the prostate gland. About 8 Gm. of tissue was resected, after which the patient voided urine normally.

Henline⁵³ states that each of the three main types of prostatic operation—prostatic resection, suprapubic prostatectomy and perineal prostatectomy—has its place, yet none should be used to the exclusion of the others. The origin, the extent and the location of prostatic disease always should be considered in selection of the proper operative approach to relieve the patient completely and permanently of his prostatic disease. Prostatic calculi can be more completely removed by subtotal perineal prostatectomy with less morbidity and more nearly permanent cure than by other methods. Perineal exposure with removal of the posterior lobe of the prostate gland is the only method by which an early malignant neoplasm of this portion of the prostate gland can be removed. Newer perineal prostatic operations permit adequate control of hemorrhage, offer a means of complete removal of the diseased prostate gland, often prevent postoperative morbidity and provide greater assurance of permanent lasting relief from prostatism.

Resection.—Nesbit and Conger,⁵⁴ in discussing their studies on the loss of blood during transurethral prostatic resection, state that the excessive loss of blood which occurs during any surgical procedure tends to increase the hazard of operation and to influence adversely postoperative morbidity. Candidates for prostatectomy frequently are elderly and debilitated men who often have some degree of renal insufficiency. Excessive loss of blood resulting from well executed transurethral resection among such patients may impair the general recuperative powers and resistance to infection, even though the patients escape immediate surgical shock. To secure data on the actual loss of blood during operations among these patients, a series of 100 consecutive cases in which transurethral resection was done was studied, and the loss of blood was estimated.

53. Henline, R. B.: The Surgical Treatment of Prostatic Disease, J. A. M. A. **117**:2030-2034 (Dec. 13) 1941.

54. Nesbit, R. M., and Conger, K. B.: Studies of Blood Loss During Transurethral Prostatic Resection, J. Urol. **46**:713-717 (Oct.) 1941.

In this series of cases a fair cross section of prostatic disease was obtained. There were 71 cases of benign prostatic hypertrophy, 21 cases of carcinoma of the prostate gland and 8 cases of contracture of the vesical neck. In 3 cases, reresection was done. Thirty-nine patients were operated on by the chief of the service; the rest were operated on by the resident surgeons.

Operative losses of blood varied greatly; the amounts ranged from as low as 4 cc. in a case of contracture of the vesical neck to 1,254 cc. in a case of particularly vascular benign hypertrophy. The average loss of blood in this series was 169 cc. Forty-six per cent of all patients lost less than 100 cc. of blood. These were patients who had smaller glands and median bars. Twenty-two per cent of the patients lost more than 250 cc. These patients had larger prostate glands (average, 35.4 Gm.), and the condition in all was benign, except in 4 who had cancer.

Determinations of the postoperative loss of blood were not carried out in Nesbit and Conger's series because urinary pigments made colorimetry inaccurate. They say, however, that in 1937, Hubly studied a series in which transurethral resection had been done in 53 cases at the Mayo Clinic and that he estimated both the operative and the twenty-four hour postoperative loss of blood by spectrophotometric and photometric methods. He found, they say, that patients lost about two-thirds again as much blood during the first twenty-four hours postoperatively as was lost during the operation itself. Nesbit and Conger believe these figures to be highly significant and speculate that the total loss of blood approximated perhaps twice the operative loss. Thus, they conclude that the 22 per cent of their patients who lost more than 250 cc. of blood during operation, as previously noted, eventually suffered a significantly high loss of blood.

Carcinoma.—Herbst⁵⁵ discusses the effects of estradiol dipropionate and diethylstilbestrol on malignant prostatic tissue. These substances apparently relieve the pain caused by local prostatic malignant tissue and metastasis of carcinoma to bone and modify the physiology of breast and prostatic tissue in a demonstrable manner. The ultimate result of this action was not predictable at the time of Herbst's report, and pathologic microscopic studies have not been possible. Relief of dysuria and nocturia and reduction in the amount of residual urine are early responses to this form of treatment, he states.

As time goes on, Herbst says, it is to be hoped that observations such as those he mentions will serve to stimulate progress in specific control of tissue by the administration of these or other yet to be produced

55. Herbst, W. P.: The Effects of Estradiol Dipropionate and Diethyl Stilbestrol on Malignant Prostatic Tissue, *Tr. Am. A. Genito-Urin. Surgeons* **34**:195-202, 1941.

substances. It should be fully realized in the meantime, however, that the complexity of the biochemical problem is such that it may be a long long time before completely satisfactory control of tissue can be an accomplished fact.

De Vries,⁵⁶ in discussing the differential diagnosis of carcinoma of the prostate gland with skeletal metastasis and osteitis deformans, states that digital examination of the prostate gland per rectum will be sufficient for diagnosis in 90 per cent of the cases; but because some malignant lesions originate and are situated in parts of the prostate gland other than the posterior lobe, cystoscopy should not be neglected. Biopsy may be desirable for confirmation of the diagnosis, but unless results are positive, biopsy in itself should not be relied on. Aspiration biopsy is less reliable than other methods. Roentgen examination of the bones should be extensive and directed specifically to the study of bone, both distribution and local appearance being diagnostic factors. So far as distribution is concerned, although the spinal column, the pelvis and the long bones may be affected by either condition, a lesion of the skull is most likely to be Paget's disease, and a costal lesion is most likely to be carcinoma. In the matter of local appearances, thickening, increase of coarse trabeculations, bowing and deformity, increased cortical density and decrease of the marrow space are the important observations in Paget's disease; whereas absence of these signs with spotty areas of increased density, decreased density or both present is the significant characteristic of metastatic carcinoma of the prostate gland. It is well to remember also the possibility that both lesions can occur simultaneously in the same person.

Leiomyosarcoma.—Prince and Vest⁵⁷ report a case of leiomyosarcoma of the prostate gland and state that leiomyosarcoma is a definite entity which differs pathologically and clinically from other types of sarcoma of the prostate gland. Among adult persons, leiomyosarcoma is of a somewhat lower degree of malignancy than is sarcoma of the prostate gland of other types. The average duration of life in the acceptable cases of leiomyosarcoma of the prostate gland has been found to be three and two tenths years among patients more than 20 years old and two and a half months among patients less than 20 years old. As far as Prince and Vest know, they say, this is the first instance in which the diagnosis has been made preoperatively and in which complete surgical

56. de Vries, J. K.: *The Differential Diagnosis of Carcinoma of the Prostate with Skeletal Metastases and Osteitis Deformans (Paget's Disease of Bone)*, J. Urol. **46**:981-996 (Nov.) 1941.

57. Prince, C. L., and Vest, S. A.: *Leiomyosarcoma of the Prostate: Report of a Case and Critical Review*, J. Urol. **46**:1129-1143 (Dec.) 1941.

removal of the prostate gland has been carried out intentionally for sarcoma. The functional results which followed radical operation in their case were excellent, and the patient was apparently completely well and free from metastasis a year after the operation.

Abscess.—Hamer and Wishard⁵⁸ report an unusual case of prostatic abscess. The patient, 64 years old, who had low grade nonspecific prostatitis, returned after a vacation complaining of cloudy urine and moderate irritability of the bladder. Massage of the prostate gland yielded the usual secretion, which contained 50 pus cells, more or less, per field under the high power objective. There was no residual urine. After gentle massage of the prostate gland, the patient had a chill. Inflammatory enlargement of the left lobe of the prostate gland was noted, but no evidence of fluctuation could be found. Each rectal examination was followed by chills and fever. Sulfanilamide drugs improved the clinical picture not at all. Within another week, signs of cardiac enlargement appeared; these were followed shortly by "congestive heart failure and terminal pneumonia within eighteen days of the onset." Necropsy disclosed a prostate gland slightly larger than normal, in the left lobe of which was a completely sealed-off abscess 5 mm. in diameter. Smears of material obtained from this abscess contained gram-positive cocci. Small, thrombosed veins and many lymphatic glands were found along the course of the great vessels, as far as the mediastinum. Acute fibrinous pericarditis and an incidental aneurysm of the aortic arch also were seen.

URETHRA

Carcinoma.—Wishard⁵⁹ has brought the bibliography of primary carcinoma of the male urethra up to date through May 31, 1941. The total number of instances substantiated by biopsy is 166. Wishard includes an additional instance in which carcinoma of the male urethra was treated by radium, roentgen rays and electrocoagulation with apparent success (for two years at least) without evidence of recurrence. He makes no claim, however, of originality for the method.

Dodson⁶⁰ reports 3 cases of carcinoma of the urethra. In the first of these, the patient was an elderly man whose urethra had been divided and transplanted into the scrotum because of stricture which had

58. Hamer, H. G., and Wishard, W. N., Jr.: An Unusual Case of Prostatic Abscess, *Tr. Am. A. Genito-Urin. Surgeons* **34**:261-264, 1941.

59. Wishard, W. N., Jr.: Primary Carcinoma of the Male Urethra, *Tr. Am. A. Genito-Urin. Surgeons* **34**:265-271, 1941.

60. Dodson, A. I., in discussion on papers of Barringer, Nesbit and Cummings,⁴⁷ Hamer and Wishard⁵⁸ and Wishard,⁵⁹ *Tr. Am. A. Genito-Urin. Surgeons* **34**:274-275, 1941.

followed gonococcic infection. When he was seen he was almost moribund, and external ureterostomy was done for drainage in the hope that some sort of treatment of the tumor could be instituted later. He died rather quickly. Necropsy disclosed that squamous cell carcinoma had involved the urethra and the scrotum.

The second patient had no history of gonorrhea or previous stricture. He had consulted a urologist, who had resected the prostate gland; this he believed was the source of the bleeding. Later, periurethral abscess developed. Resection of the perineal portion of the urethra, including the penis, was done, and repair was made by the turning down of a flap of the urethra posteriorly and utilization of the subcutaneous structure of the scrotum to fill in and cover over in front.

The third patient had a history of stricture which had been treated after an attack of gonorrhea and which occurred in association with periurethral abscess. Resection and reanastomosis of the corpora and the urethra were done for this patient.

An outstanding feature in these 3 cases was an abscess at the site of the cancer, and this abscess was similar to the type of perineal abscess that is found in cases of advanced stricture of the urethra.

TESTES

Tumors.—Hinman, Johnson and Carr⁶¹ state that all testicular tumors should be treated by immediate orchidectomy, followed by adequate roentgen therapy. Radical removal of the regional lymph zone has been discontinued because careful study of the records of all their patients throughout the years convinced them that not infrequently metastasis occurs across the midline or even above the surgically available lymph zone before it is demonstrable in the chain of lymph nodes which formerly was removed.

The presence of abnormal amounts of hormone in the urine suggests a bad prognosis.

It seems evident that all malignant testicular tumors are so closely related that only a simple clinical classification of them is justifiable.

The malignancy of a given testicular tumor depends on the degree of the differentiation of cells, and this is not constant in any given case.

Transplantation.—Kearns⁶² carried out autoplasmic testicular transplantation for a patient 23 years old, after accidental castration. The

61. Hinman, F.; Johnson, C. M., and Carr, J. L.; The Clinico-Pathologic Classification of Tumors of the Testis in Relation to Prognosis, *Tr. Am. A. Genito-Urin. Surgeons* 34:211-225, 1941.

62. Kearns, W. M.: Testicular Transplantation: Successful Autoplasmic Graft Following Accidental Castration, *Ann. Surg.* 114:886-890 (Nov.) 1941.

patient's testes, which after accidental removal had been preserved, were then transplanted. Each section, which was about 2 mm. thick, was implanted in the scrotal wound and covered with the flaps of the remaining scrotal skin. One section of epididymis also was implanted. Successful graft resulted. Observation of this patient for two and a half years demonstrated that regeneration of the prostate gland and normal sexual function had resulted and that normal results of clinical and laboratory tests had persisted. Kearns recommends this procedure for replacement of testicular tissue which is lost in warfare.

Ectopy.—Thompson and Heckel⁶³ state that there are two causes of failure of descent of the testis: (1) glandular deficiency and (2) anatomic abnormalities.

Since the testis can function normally only when it is enclosed in the scrotum, Thompson and Heckel are of the opinion that it is logical to assume that the earlier it is brought into the scrotum, the more likely it is to be normal. By means of glandular therapy it is possible to determine at an early age whether or not operative procedures will be necessary. If there is no mechanical obstruction, the testis will descend by means of glandular therapy alone. If it does not descend, operative procedures will be necessary and can be facilitated by enlargement of the parts as produced by glandular therapy. Chorionic gonadotropin is the most satisfactory therapeutic agent in most instances. Treatment involves use of the combination of glandular therapy and surgical procedures. The age of the patient and the situation of the testis exert some influence on the success of glandular therapy. The incidence of successful results is higher before than after the patient has reached the age of puberty.

Thompson and Heckel were able to produce testicular descent in only 2 of 34 cases in which the location of the testes was intra-abdominal. The majority of successful results were obtained when the testes were located either in the inguinal canal or outside the canal. Thompson and Heckel are uncertain as to how early treatment should be carried out, but they believe observations suggest that therapy should be commenced when the patient is still at an early age.

It is important, they say, to distinguish between true cryptorchidism and pseudocryptorchidism (migratory testes). Migratory testes descend spontaneously at the time of puberty and require no treatment. The inclusion of migratory testes in studies of glandular therapy has tended to exaggerate the percentage of successful results obtained in true cryptorchidism, Thompson and Heckel believe.

63. Thompson, W. O., and Heckel, N. J.: Endocrine Treatment of Cryptorchism, J. A. M. A. **117**:1953-1956 (Dec. 6) 1941.

Counseller⁶⁴ states that the age of the patient when he presents himself for the treatment of cryptorchidism has a definite influence on the type of surgical procedure to be used. The site and the position of the testis also are determining factors. A much higher incidence of indirect inguinal hernia on the affected side was noted than had been previously reported, although when the group is considered as a whole the incidence was essentially the same as that noted by previous authors.

Surgical procedures for the correction of cryptorchidism must be varied to suit the particular case with regard to unilaterality, bilaterality and the position of the testes. When it is desirable to develop a scrotum and to maintain the testes for indefinite periods in a fixed position without tension, the Meyer-Torek operation is most satisfactory. In most other instances, the Cabot operation is generally applicable. In a relatively few cases in which there is a normally developed scrotum and in which the testes can be easily placed in the scrotum, the Bevan operation may be indicated.

Castration must be considered as a surgical procedure when cryptorchidism is encountered. Castration usually is done for atrophy, for inability to add sufficient length to the cord, for tumor or for previous injury. It is not commonly done when the patient is in the first and second decades of life, but generally is performed when he is beyond the third decade.

Endocrinotherapy for cryptorchidism should be confined to a relatively few patients and should be employed, even then, only if spontaneous descent seems improbable. It can be used with benefit in cases of hermaphroditism or hypogonadism, Counseller says.

Heckel⁶⁵ states that, in contrast to the enthusiastic reports of highly successful results from hormonal therapy for cryptorchidism, he has not been able to bring undescended testes into the scrotum in more than 20 per cent of the total number of cases. He has never been able to cause descent in any instance of intra-abdominal testes.

It seems that in the proper management of the problem of undescended testes, two classifications should be considered. In the first group are those patients who have an undescended testis or testes associated with some endocrine disturbance, such as Fröhlich's syndrome, hypopituitarism or genital infantilism from whatever cause. In this group endocrinotherapy plays an important role in the management of the condition. The type of endocrine preparation to use depends on the

64. Counseller, V. S.: Ten Years' Experience in the Management of Cryptorchidism, *J. Urol.* **46**:722-731 (Oct.) 1941.

65. Heckel, N. J., in discussion on Counseller.⁶⁴

ability of the testes to respond to stimulation. If the testes can respond to stimulation, then chorionic gonadotropin is the therapeutic agent of choice. If not, androgens should be used.

In summary, Heckel says that it seems that the high percentage of good results (60 to 70 per cent, on an average) reported from the use of endocrinotherapy for cryptorchidism is greatly exaggerated and that, as Counseller has pointed out, perhaps the reason for this is the incorrect diagnosis of undescended testes and the inclusion of the so-called migratory testes, or those which migrate in and out of the scrotum and tend to remain in the scrotum at or near the time of puberty. Patients with this sort of cryptorchidism make up the second group. Heckel says that no treatment of migratory testes is indicated. The greatest field of usefulness of endocrinotherapy for undescended testes is among those patients who have some type of endocrine disturbance associated with this condition and among those in whom the failure of descent is not due to mechanical factors. The management of true undescended testes, however, is still a surgical procedure.

Sex Hormones.—Heckel⁶⁶ states that alpha estradiol benzoate, like testosterone propionate, produces sterility in man. The degenerative changes in the seminiferous tubules caused by these two substances are similar. Whereas testosterone propionate has no effect on the volume of seminal fluid, alpha estradiol benzoate produces a spectacular decrease in its volume. Since the seminal fluid in man is composed mostly of the secretions from the prostate gland and the seminal vesicles, Heckel has deduced that the cause for this decrease in volume is due to the influence of this material on the secretory mechanism of these two glands. Other untoward effects observed to result from the use of alpha estradiol benzoate were: hypertrophy of the breasts, enlargement of the nipples and the development of impotency.

Tumor.—Gilbert⁶⁷ analyzes 58 of the detailed reports concerning a total of 65 patients among whom malignant tumor of the testis developed after orchidopexy. The interval between orchidopexy and development of the tumor averaged twelve years for the unicellular type and five years for teratoid tumor. In 49 cases of the entire group in which it was recorded, the average interval between orchidopexy and recognition of the tumor was ten years. The duration of recognized tumor growth,

66. Heckel, N. J.: A Comparative Study of the Effect of Sex Hormones upon the Function of the Human Testes, *Tr. Am. A. Genito-Urin. Surgeons* 34:237-247, 1941.

67. Gilbert, J. B.: Studies in Malignant Testis Tumors: V. Tumors Developing After Orchidopexy; Report of Two Cases and Review of Sixty-Three, *J. Urol.* 46:740-747 (Oct.) 1941.

to the time of surgical intervention, as stated in 45 cases, averaged sixteen months. There were 34 unicellular tumors and 19 teratoid tumors. The remaining 12 tumors were either of miscellaneous types or not definitely classified. In 54 cases (83 per cent), the tumor-bearing testicle was situated in the scrotum, whereas in 11 (17 per cent), it was located ectopically (7 inguinal and 4 abdominal). Among the majority of the patients (43 or 66 per cent), the tumor was primary and operable, whereas among only 15 (23 per cent) it was inoperable on admission of the patient. Of the 34 patients who had unicellular tumors, 16 (47 per cent) were alive and apparently well one and a half years later, whereas 5 (15 per cent) were alive three years later, and 1 of these was alive five years after surgical intervention. Of the 19 patients who had teratoid tumors, 3 (17 per cent) lived three years after the operation, and only 1 of these was alive five years after the operation.

Gilbert says the survival rate in this group is poor. Only two authors have reported arrest of metastatic disease by means of combined surgical treatment and irradiation, and two others have reported five year survivals achieved by operation alone; in 1 case the lesion was seminoma and in the other teratoma.

On the basis of the results of his study, Gilbert concludes that the ectopic testis should be adequately fixed in the normal scrotal position. Surgical replacement to the abdomen is condemned. The predominating pathologic type is unicellular. Teratoid tumors in his series developed seven years earlier than unicellular tumors after orchidopexy and were consistently more fatal. Surgical trauma incidental to testis fixation and herniorrhaphy does not appear to favor the genesis of tumors.

URINARY CALCULI

Sanford and Barnhart⁶⁸ state that renal stones which are studied and classified preoperatively as being too large to pass down the ureter should be removed surgically unless serious contraindications to operation are present. The danger of infection and the potential threat that a stone might move to an obstructive position with the almost immediate production of acute symptoms is constantly present. In contrast to this anticipated occurrence, appreciation of the opposite possibility also is important. A patient who has a single stone of fairly large size situated in the true pelvis of the kidney may be surprisingly free from symptoms. Delayed operation, intentional or otherwise, is

68. Sanford, J. H., and Barnhart, W. T.: The Surgical and Nonsurgical Management of Renal and Ureteral Calculi, *J. Urol.* **46**:1061-1069 (Dec.) 1941.

occasionally followed by disaster. Some months later the stone may have migrated down the ureter and silently destroyed the kidney. Unilateral or bilateral branched renal calculi are conspicuously devoid of pronounced symptoms but consistent in the gradual and progressive damage to renal function which they cause. Early operation in the presence of unilateral or bilateral branched renal calculi is advisable in most cases. Sanford and Barnhart say that a large percentage of ureteral calculi that can be accommodated by the ureter are recoverable by cystoscopic manipulative methods. They say that they prefer the ureteral catheter or the use of catheters left in place for twenty-four to forty-eight hours to any other method. In cases in which infection is resistant, with partial or complete blockage of the kidney, surgical intervention is demanded after several attempts at conservative measures have failed. Delay in this type of case is hazardous. Incision of the ureteral orifice to facilitate passage of stones in the extreme lower part of the ureter has proved to be immensely valuable.

Of 200 patients with calculi in the upper part of the urinary tract seen by Sanford and Barnhart in the six years prior to their report, 64 had renal calculi, 125 had ureteral calculi and 11 had both renal and ureteral calculi. Those who had renal calculi were treated in the usual manner, i. e., by either observation or operation. In the latter case, pyelolithotomy, nephrolithotomy or nephrectomy was done. In the 125 cases of ureteral calculi, surgical removal was done in 17, and the calculus was passed or extracted from the ureter in 108 cases.

In 86.4 per cent of the cases of ureteral calculi, operation was not necessary, and Sanford and Barnhart believe that such conservatism was justified. They say, however, that the urologic surgeon can be too conservative.

UROLOGIC COMPLICATIONS

Ewert⁶⁹ states that postoperative genitourinary complications after surgical treatment of the large bowel are most common after removal of the rectal portion of the large intestine. The complications may be of such major importance that they definitely prolong the patient's convalescence. Infections of the urinary tract account for most of these complications and may be interrelated with the neuromuscular function of the bladder in many instances. Paralysis of the bladder must be treated intelligently if the upper portion of the genitourinary tract is to be spared irreparable damage. Since many patients continue to have

69. Ewert, E. E.: A Comparative Analysis of the Urological Complications Following Large Bowel Surgery, *J. Urol.* **46**:764-776 (Oct.) 1941.

pyuria after they are dismissed, even though they may have no symptoms, persistent reexamination to determine the cause and the treatment is necessary for months. The cure of the cancer is the major role; the treatment of the urologic complications frequently is the minor one.

Seaman and Binnig⁷⁰ say that urologic complications occurring in the presence of cancer of the rectum and due either to the disease itself or to the operation incident to the removal of the neoplasm are relatively common. They vary in occurrence and severity and are more often than not caused by destruction of sympathetic or parasympathetic pathways or some degree of trauma and possibly also by infection. Infection is a common accompanying problem, because of the nervous disturbance and because of the altered position of the floor of the bladder in the pelvis.

An appraisal of the present operative technic is suggested for avoidance of trauma to the lower part of the urinary tract and its nerve supply. There is apparent evidence that the suggestion has merit. The authors emphasize the importance of urologic orientation before and after operations, and they stress the need for the carrying out of cystometric studies for each patient. The present day concept of neuroanatomy and neurophysiology is offered as a background to understanding the mechanism of dysfunction of the bladder.

VAGINITIS

Rice, Cohn, Steer and Adler⁷¹ report results of their recent investigations on gonococcic vaginitis. Since the inception of their study, 381 (22.2 per cent) of 1,715 children they examined were found to have gonococcic vaginitis. The infected children were examined once a week until the results of diagnostic laboratory procedures were negative and remained thus for about eight successive weeks, after which the children were examined at monthly intervals.

Nonspecific vaginitis and gonococcic vaginitis can be distinguished only by means of smear and/or culture. Culture is far superior to the making and examining of smears, especially if the chronic stage of the infection is present.

It was arbitrarily agreed by the authors that children, to be considered cured, must be clinically normal and that at least seven smears and cultures made consecutively during a period of at least sixteen

70. Seaman, J. A., and Binnig, C.: Urological Complications of Cancer of the Rectum, *J. Urol.* **46**:777-787 (Oct.) 1941.

71. Rice, J. L.; Cohn, A.; Steer, A., and Adler, E. L.: Recent Investigations on Gonococcic Vaginitis, *J. A. M. A.* **117**:1766-1768 (Nov. 22) 1941.

weeks must contain no gonococci. Prolonged study revealed that this criterion was satisfactory for 92.2 per cent of the 204 patients studied intensively.

Forty-one children were observed who did not receive any form of treatment. Some recovered within a short time; 54 per cent recovered by the tenth week, and 87 per cent recovered by the twenty-eighth week, after the beginning of observation. This, the authors believe, is definite evidence that spontaneous cure of the disease may occur among the majority of patients.

Thirty-three children were treated with estrogenic substances (amniotin and diethylstilbestrol). The 12 (36 per cent) who were cured were treated for an average of fifty-four and five-tenths days. Comparison of results with the results obtained in control series shows that, bacteriologically, cure was no more frequent among patients who received this form of therapy than it was among the untreated patients. Definite clinical improvement, however, followed shortly after the institution of treatment.

Fifty-three children were treated with sulfanilamide. The 23 (43 per cent) who were cured were treated for an average of nine and six-tenths days. This drug gave definitely better results than would be expected without treatment.

Because the results of therapy obtained with each drug were approximately the same, the 20 children treated with sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) and the 57 treated with sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) were combined into a single group. The 67 (87 per cent) who were cured received treatment for an average of six and seven-tenths days. These drugs were effective against rectal infection when it was present. Sulfathiazole appeared to be the drug of choice, because it produced fewer toxic reactions (nausea and vomiting) than did sulfapyridine. For the present, the authors suggest that children receive $\frac{1}{2}$ grain (0.032 Gm.) per pound (0.5 Kg.) of body weight per day, with a maximum of 30 grains (2.0 Gm.) per day for from seven to ten days.

Vaginitis is generally believed to be extremely contagious, requiring only superficial contact for its transmission. Outbreaks in epidemic form have been described. Rice, Cohn, Steer and Adler, however, say that the question of widespread dissemination of this disease in public places requires reconsideration. In more than five years of search no evidence was found of an epidemic in a New York school, although many children who had recently acquired infections had attended these schools before a diagnosis was made. During the course of this study

no instance of an epidemic in any institution or orphanage was discovered.

URINARY ANTISEPTIC AGENTS

Therapy with Sulfanilamide and Its Derivatives.—Carroll, Kappel and Allen ⁷² state that sulfathiazole and the sodium salt of sulfathiazole are found to be of little value in the treatment of prostatitis. In the treatment of pyelitis, pyelonephritis, ureteritis, cystitis due to urinary retention, cystitis associated with Hunner's ulcers and nonspecific urethritis, sulfathiazole and its sodium salt, although they are valuable adjuncts in treatment, do not provide permanent cure in a large percentage of cases of these diseases. Relief of these conditions depends on proper diagnosis of the causative factors involved and the correction of them.

The use of the drug is limited also, because of the toxic or allergic reactions to it which comprise 15 per cent of the urinary infections encountered. The confusion created by so-called drug fever and the uremic symptoms caused by the drug act as deterrents to the prescription of this drug. The mode of application has been enlarged from that of oral administration to that of local application of the powder in wounds postoperatively and into necrotic and abscessed cavities as well as to ulcers and infections about the genitalia.

Deakin and Patton ⁷³ state that approximately 19 out of 20 men who have gonorrhea can be rendered noninfectious by the oral administration of 20 Gm. of sulfathiazole in a five day period. Sulfathiazole is more efficient than sulfanilamide or sulfapyridine in the oral treatment of gonorrhea among men. When this dosage is employed, risk in the use of sulfathiazole as a form of ambulatory treatment of gonorrhea is minimal. Lack of cooperation on the part of the patient, previous therapy with the sulfanilamide drugs and the presence of severe complications before treatment are the chief causes of chemotherapeutic failure in this particular disease.

Herrold, ⁷⁴ in discussing Deakin and Patton's paper, states that he and John Henry had administered sulfathiazole to approximately 400 male patients suffering from gonorrhea at the Illinois Social Hygiene

72. Carroll, G.; Kappel, L., and Allen, H.: Sulfathiazole and Its Sodium Salt: Effectiveness and Limitations in Clinical Practice, *J. Urol.* **46**:1033-1042 (Nov.) 1941.

73. Deakin, R., and Patton, J. F.: Sulfathiazole in the Treatment of Two Hundred Cases of Male Gonorrhea, *J. Urol.* **46**:1043-1048 (Nov.) 1941.

74. Herrold, R. D., in discussion on papers of Prien, Crabtree and Frondel, Carroll, Kappel and Allen and Deakin and Patton, *J. Urol.* **46**:1049-1050 (Nov.) 1941.

Clinic. They completed their study on the group treated between May 15 and Dec. 15, 1940. There were 271 patients in this group, of whom 148 received exactly the same dosage as members of the group of Deakin and Patton, namely, 4 Gm. a day for five days. Herrold says that he and Henry had accepted this as their standard dosage schedule. Two hundred and six of the patients were seen for periods longer than thirty days, and 149 (about 55 per cent) were seen for periods longer than sixty days. Hence, there remained 65 patients (approximately 24 per cent) who were transferred, left the city or deliberately lapsed treatment before they had received it for thirty days.

Relapse or reinfection was noted among 36 patients during the course of observation, so that if everything is taken into consideration, it is believed that between 80 and 90 per cent of male patients with gonorrhea can be cured by the administration of one course of sulfathiazole. Herrold says that in the clinic in question, local treatment is given by the physicians because it has aided in obtaining the cooperation of the patients. It has been found also that when sulfathiazole is used, a higher percentage of failures occurs among patients in whom previous treatment with other sulfanilamide drugs has failed to cause improvement. Little can be expected from the practice of repeating the course of treatment with sulfathiazole for patients with infections which clearly have been refractory to sulfanilamide drugs, but Herrold says that he does not agree that a second course should not be instituted for those patients who previously have received no chemotherapy other than one course of sulfathiazole and who have experienced clinical relapse within a week after completion of the first course. A number of such patients, he says, have been cured by receiving a second course of therapy with either sulfapyridine or sulfathiazole.

Herrold has seen also many patients who did not respond clinically to therapy with sulfanilamide during the first ten days of their infection; when, however, the medication was changed to either sulfapyridine or sulfathiazole, prompt favorable response was obtained, a response which was similar to that obtained among patients to whom chemotherapy had been administered previously. Sulfathiazole is the drug of choice over sulfapyridine because of the smaller incidence of certain toxic reactions, particularly those referable to the gastrointestinal tract, which accompany its use.

Fletcher, Gibson and Sulkin⁷⁵ carried out a carefully controlled study among 194 hospitalized female patients with gonorrhea. Two methods of treatment were employed. The first consisted of the oral

75. Fletcher, P. F.; Gibson, O. J., and Sulkin, S. E.: Sulfathiazole in the Treatment of Gonorrhea in Women, *J. A. M. A.* **117**:1769-1773 (Nov. 22) 1941.

administration of 60 grains (4 Gm.) of sulfathiazole daily for five days and the insertion of a vaginal suppository containing beta lactose and boric acid. The suppository was inserted once a day for twelve consecutive days. The second method of treatment consisted of the administration of the same dose of sulfathiazole but omission of the vaginal suppository.

Toxic manifestations were noted in 13 cases (6.7 per cent) and were sufficiently severe in 2 of them to necessitate termination of treatment. The most pronounced reactions observed were manifested as a painful urticarial rash in 1 case and as uncontrollable nausea and vomiting in a second case. All cutaneous manifestations disappeared within seventy-two hours after the administration of the drug had been discontinued.

Every case was classified as chronic gonorrhea with the exception of 2 in which there was acute inflammation of the cervix, the urethra and both adnexa associated with a severe febrile reaction. In the cases classified as chronic gonorrhea there were no symptoms.

Forty-five per cent of the patients had a gonorrheal infection of the cervix alone. In 12 per cent, only the urethra was involved, whereas in 43 per cent both cervical and urethral infections were present. "Every patient in whom the pelvic adnexa were present showed some type of chronic inflammatory condition," the authors remark.

Detailed analysis of the results obtained in the two groups of patients revealed that beta lactose therapy had had no influence on the treatment of gonococcic infection. The authors conclude:

. . . Ninety-one and two tenths per cent of the total number of patients under observation at the end of the "quarantine parole" period (twelve weeks) were considered "clinical cures." It may therefore be assumed that sulfathiazole in the treatment of gonococcic infections in the female is highly effective in a great majority of cases.

Peterson and Beuchat⁷⁶ report the following impressions after studying and treating 178 patients with gonorrhea:

About half of the patients who receive sulfanilamide will have an immediate adequate response and will be cured. The other half will have an inadequate response.

It appears that the immediate adequate response of the patient to sulfapyridine is greater than his response to sulfanilamide. Sulfapyridine therapy in cases in which the infection has resisted sulfanilamide is efficacious. Among patients with gonorrheal epididymitis and arthritis, the response to sulfapyridine therapy is much better than the response to sulfanilamide.

76. Peterson, D. B., and Beuchat, E. S.: Treatment of Gonorrhea at Fitzsimons General Hospital: A Study of Cases from Sept. 1, 1938 to Oct. 31, 1940. *J. A. M. A.* **118**:129-132 (Jan. 10) 1942.

Artificially produced fever is the most efficacious treatment for gonorrhea but has definite disadvantages in that it is expensive and is of danger to the patient. This danger is increased if previous medication with sulfanilamide has been carried out, and almost all patients with gonorrhea have been so treated before they reach a hospital where fever therapy is available. Fever is the standard of good treatment in cases of gonorrheal arthritis.

Patients who do not exhibit an adequate response to initial treatment with sulfanilamide by the fourth day should receive either fever therapy or sulfapyridine.

Welebir and Barnes⁷⁷ treated 200 patients who had bacillary infection of the urinary tract with sulfacetimide (paraaminobenzenesulfonylacetylimide). The percentage of recoveries was 85.5; 12.5 per cent of the patients exhibited improvement, and 2 per cent exhibited no response to the drug.

Sulfacetimide has been more effective in the treatment of this type of infection of the urinary tract than have sulfanilamide and the mandelates. In 80.9 per cent of the cases in which the infection had been resistant to sulfanilamide, recovery occurred when sulfacetimide was administered; in 73.3 per cent of the cases in which the infection had been resistant to the mandelates and in all in which it had been resistant to sulfathiazole, recovery occurred when sulfacetimide was used.

There were toxic reactions in 4 per cent of the patients in this series. After discontinuance of the use of the drug, the reaction disappeared within from one day to six days.

The results of this clinical investigation show, the authors say, that sulfacetimide is effective and superior to other sulfanilamide drugs in the treatment of bacillary infections of the urinary tract.

Kornblith, Jacoby and Chargin⁷⁸ treated a series of 175 ambulatory patients encountered consecutively and having chancroid infection with sulfanilamide and sulfathiazole.

Identification of the haemophilus of Ducrey on smears stained by the Unna-Pappenheim method was found to be the most important single diagnostic criterion of chancroidal infection. The haemophilus of Ducrey was identified in 88.5 per cent of the cases in smears made routinely with material obtained from chancroidal ulcers. The intradermal reaction to Ducrey vaccine proved to be specific and was found to be positive in about 95 per cent of cases. The authors write:

77. Welebir, F., and Barnes, R. W.: The Use of Sulfacetimide in Bacillary Infections of the Urinary Tract, *J. A. M. A.* **117**:2132-2135 (Dec. 20) 1941.

78. Kornblith, B. A.; Jacoby, A., and Chargin, L.: Chancroid: Treatment with Sulfathiazole and Sulfanilamide, *J. A. M. A.* **117**:2150-2153 (Dec. 20) 1941.

The Ducrey vaccine is more important when the results are negative, to exclude active chancroidal disease. When the reaction is positive it often indicates a past, healed infection.

The reaction to Ducrey vaccine remained positive in all cases after complete healing of the active lesion had taken place.

Chancroidal buboes were present in about 42 per cent of the cases.

Sulfanilamide was administered orally to 150 patients for fourteen days; a total of 45.6 Gm. (760 grains) in divided doses was found to be adequate. Sulfathiazole was administered orally to 25 patients for ten days; a total of 20 Gm. (300 grains) in divided doses sufficed.

All definitely proved chancroidal infections were healed by means of chemotherapy. Surgical measures of any description were contraindicated and found unnecessary. Aspiration of the contents of large inguinal abscesses was found to be sufficient in some cases. Spontaneous absorption of small abscesses took place in 5 cases during chemotherapy. The local application of sulfathiazole powder healed superficial chancroidal ulcerations. Two patients suffered a relapse, but the lesion responded promptly to oral therapy with sulfathiazole.

More than half (54 per cent) of the patients in the series were found to be infected with two, three or four venereal diseases during their observation.

Therapy with sulfanilamide and its derivatives can be used as a therapeutic test in the differential diagnosis of chancroid.

Cook⁷⁹ reports the results of recent studies with sodium sulfathiazole. The advantages of this form of the drug over its parent substance are: 1. It is more rapidly absorbed. 2. It is less toxic. As it is absorbed more rapidly, it also is excreted more rapidly. Early in the work on sulfanilamide and its derivatives, the use of much smaller doses than were used elsewhere in treating infections of the urinary tract was advocated at the Mayo Clinic. In cases of impaired renal function, sodium sulfathiazole can be used more easily than can other derivatives of sulfanilamide.

The drug was administered to approximately 200 patients with infections of the urinary tract. Every type of organism was present, as well as all types of pathologic change. The gram-negative bacilli are affected equally favorably from the standpoint of therapy, except for *Pseudomonas*, which is most obstinate to treatment. The gram-positive cocci, with one exception, all are affected satisfactorily, particularly the staphylococci and the micrococci. *Str. faecalis* is not affected by this drug; this indicates again that this organism is resistant to sulfanilamide and its derivatives. Certain coexisting pathologic changes, such as

79. Cook, E. N.: Sodium Sulfathiazole in the Treatment of Infections of the Urinary Tract, Proc. Staff Meet., Mayo Clin. 16:717-718 (Nov. 5) 1941.

tumor, calculi and obstruction, will definitely inhibit the action of the drug. This has been found to be true of all other urinary antiseptic agents.

A dose of 20 to 60 grains (1.3 to 4 Gm.) was used daily, and more recently, Cook says, it has not been more than 30 grains (2 Gm.). The drug was administered for six to ten days.

Toxic reactions have been almost nonexistent—a few patients complained of nausea, which usually disappeared within twenty-four to forty-eight hours. Cutaneous reactions were absent except in 2 cases. In both of these cases, the drug apparently produced reactions manifested by fever, general malaise, headache and nausea, as well as by dermatitis. Administration of the drug had to be discontinued in these cases. In few patients was there any elevation of temperature.

The interesting observation after a clinical trial of sodium sulfathiazole was the rather rapid relief of symptoms that occurred after its administration. Cook says that given to a patient suffering with burning, frequent micturition and dysuria, the drug will bring about complete or almost complete relief of symptoms within twenty-four to forty-eight hours in most instances. Cook believes that the rapid absorption and excretion of the drug are responsible for this rapid relief of symptoms.

Prentiss and Kanealy⁸⁰ report results of a clinical study of the efficiency and toxicity of sulfacetimide in the treatment of infections of the urinary tract and also results of a comparison of therapy with this drug with therapy with sulfanilamide. The subjects of this study were 135 patients, the first of a group of approximately 400 treated with sulfacetimide within the two years prior to the authors' report. All but 1 were hospitalized, but many were ambulatory.

All medication was administered orally, without an attempt at alteration of the consumption of the fluid. The daily dose for adult patients ranged from 2 to 10 Gm., the average being 4.89 Gm. The daily dose rarely exceeded 6 Gm., and the administration of larger amounts was not continued for more than a day or two. The length of treatment varied from two to twenty-three days; the average was approximately seven days. The amount of the drug administered in the course of treatment varied from 10 to 103 Gm., but the average patient received 32.3 Gm. The most common method of administration was in the amount of 1.5 Gm. given four times daily, but the same amount given three times daily was employed nearly as frequently. Ten to 15 grains (0.65 to 1 Gm.) of sodium bicarbonate was given with each dose of sulfacetimide.

80. Prentiss, R. J., and Kanealy, J. F.: Sulfacetimide or Sulamyd (Schering): Clinical Study of Efficiency and Toxicity in Urinary Tract Infections and Comparison with Sulfanilamide Therapy, *J. Urol.* **47**:11-15 (Jan.) 1942.

There were no severe reactions and only relatively few mild toxic reactions. Cyanosis developed in 5 patients, and among these, the condition of 1 was severe, although he exhibited only a trace of methemoglobin. Mild decreases in values for hemoglobin and erythrocytes were noted in 4 patients, but in no instance did anemia develop which required specific treatment or cessation of medication.

Prentiss and Kanealy conclude on the basis of this study and two previous reports on sulfanilamide therapy in a similar group of patients that sulfacetimide is less toxic and more efficient than sulfanilamide in the treatment of infections of the urinary tract.

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